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THE AMERICAN JOURNAL
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AUGUST, 1945

ORIGINAL ARTICLES

A COMPARISON OF THE BEHAVIOR OF MICROCRYSTALLINE SULFADIAZINE WITH THAT OF ORDINARY SULFADIAZINE IN MAN*

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Frequently the need arises, particularly in the treatment of children, for administration of sulfonamides orally in a liquid form. It is not possible to obtain solutions of the more effective compounds, such as sulfadiazine, because of their low solubility in water. The sodium salts are soluble, but their solutions are not permanently stable. Suspensions of the ordinary crystalline material tend to settle out rapidly, and as is shown in this paper, are inferior in some respects. In contrast, microcrystalline preparations of sulfadiazine and sulfathiazole remain suspended for weeks or even longer, and thus appear capable of providing the required fluid dosage form.

Microcrystalline sulfonamides have shown differences from ordinary sulfonamides in both pharmacodynamic behavior and therapeutic activity.[2,5,6,8,9] In general, such differences suggest that in microcrystalline form the activity is enhanced, but the information available is limited, and it is desirable that further investigations be made.

The results of such studies are presented in this paper. The rate of absorption and urinary excretion after ingestion of microcrystalline sulfadiazine† has been compared with that observed when ordinary

* This work was aided by a grant from the Research Fund for Infectious Diseases, University of Pennsylvania, Philadelphia.

† Microcrystalline sulfadiazine measures 1 x 1 x 3 microns and is approximately 1/350 of the mass of ordinary sulfadiazine crystals.

sulfadiazine was administered. The effects of food and of sucrose and flavoring material on the rate of absorption were also studied. Concentrations established in blood when patients received microcrystalline sulfadiazine have been compared with those obtained when ordinary sulfadiazine was used. Finally, the therapeutic activity of sulfadiazine in these two forms has been evaluated.

Materials and Methods. For the comparison of the behavior of microcrystalline sulfadiazine with that of ordinary sulfadiazine convalescent adult patients of the Medical Wards of the Philadelphia General Hospital served as subjects. The various preparations were examined under conditions closely comparable, with respect to type of subject, time, dosage, etc. In most instances, the same individual served as subject for comparison of different preparations. Each was given 3 gm. of the preparation being used, body weight being disregarded. Blood and urine specimens were collected at the times shown in the graphs; serum was used for the sulfadiazine determinations. These were made by the method of Bratton and Marshall[1] with the aid of a Klett-Summerson photoelectric photometer. The term "ordinary" sulfadiazine has been employed in this paper to distinguish the usual crystalline sulfadiazine, either in U.S.P. tablet form or as suspensions in water or sucrose, from the microcrystalline preparation.

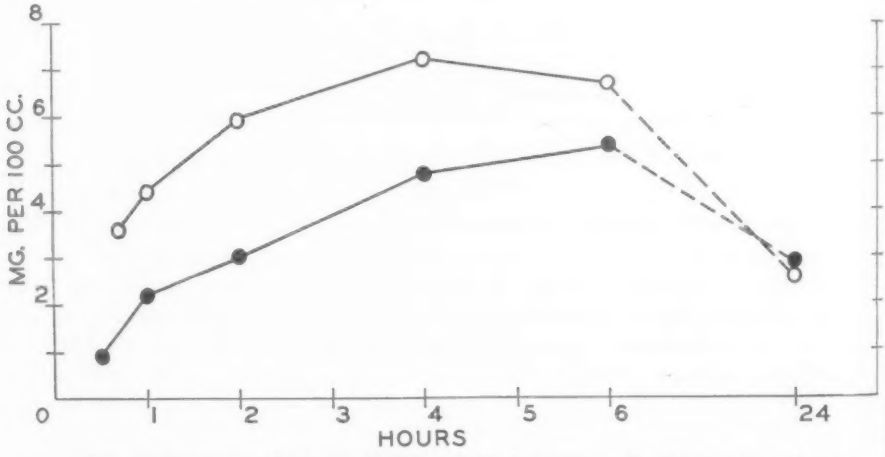

FIG. 1.—Response to microcrystalline sulfadiazine, compared with that to ordinary sulfadiazine as shown by serum sulfadiazine concentrations. Average serum sulfadiazine concentration at timed intervals after ingestion. Circles: all microcrystalline preparations, 36 subjects. Solid circles: ordinary sulfadiazine preparations, 30 subjects. Each subject received 3 gm.

Results. Figure 1 shows the trend of the concentrations of sulfadiazine in serum, following ingestion of microcrystalline sulfadiazine (upper curve) in contrast to that seen when ordinary sulfadiazine (lower curve) was ingested. When the former was used, the concentrations in serum are distinctly higher during the first 6 hours. The difference is greatest in the earlier specimens, then gradually diminishes following the 4th hour. The difference* was still significant at

* Differences were tested by Fisher's T test, as described by Goulden.[4] At the 6th hour, $p<0.05$ and >0.02.

the 6th hour, but extrapolation of the curves indicates that beyond this point the two would meet and probably intersect. At 24 hours the concentrations were the same.

Since the preparation of sulfadiazine microcrystals used (Eskadiazine)* contained sucrose and essential oils, it was thought important to evaluate the contribution of these substances to the differences between the sulfadiazine in micro- and ordinary crystalline form. For this purpose, a separate group of 7 subjects was given microcrystalline sulfadiazine (Fig. 2) suspended in water, and without the flavoring material. The response did not differ from that of the principal group of 17 subjects.

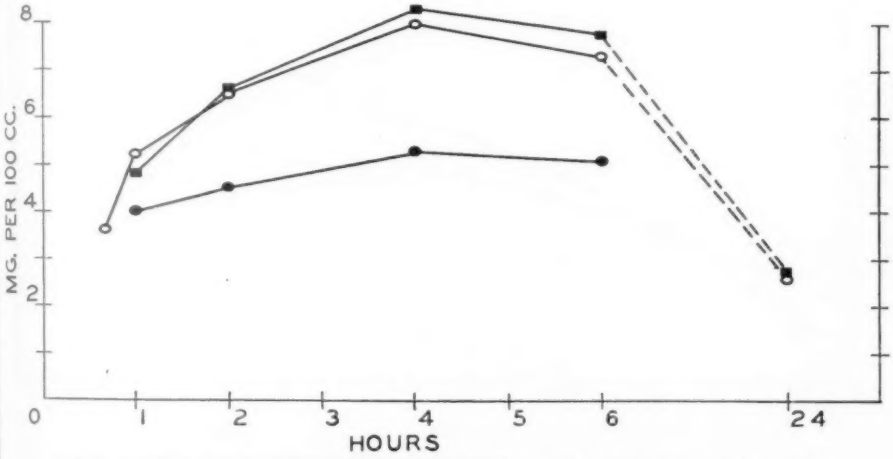

FIG. 2.—Response to microcrystalline sulfadiazine as shown by serum sulfadiazine. Effect of flavoring material and of fasting. Ovals: sucrose and essential oils present, non-fasting, 17 subjects. Solid rectangles: suspension of microcrystals in water, non-fasting, 7 subjects. Solid ovals: sucrose and essential oils present, fasting, 12 subjects.

However, fasting did exert a definite influence. Subjects who had taken their last meal 16 hours before responded with a much smaller rise in serum sulfadiazine concentration. Two hours after ingestion of the flavored microcrystalline material, the average concentration was significantly less than when the subjects had partaken of food within the preceding 2 or 3 hours. The difference persisted during the 6 hour period of observation.

The marked effect of fasting on uptake of sulfadiazine administered as microcrystals was not observed when ordinary preparations of sulfadiazine were used (Fig. 3). Likewise, inclusion of sucrose in amount sufficient to prevent settling of the crystals (about 20%) together with essential oils as flavoring, had no effect. The slower more gradual rise in serum sulfadiazine when sulfadiazine tablets were given was at first attributed to delay in disintegration of the tablet.

* This and other sulfadiazine preparations used were supplied through the courtesy of Smith, Kline & French Laboratories, Inc., Philadelphia.

However, administration of a suspension of crushed tablets failed to alter the response.

The individuals receiving preparations of microcrystals excreted more sulfadiazine in urine during the first 6 hours than did those who received plain sulfadiazine (Fig. 4). The difference was statistically significant. In subsequent periods there were smaller differences which however were not significant. The average total output in 48 hours of 11 subjects of the group receiving microcrystals was 1.999 grams and that of 10 subjects who received sulfadiazine was 1.699 grams. This difference likewise was not significant.

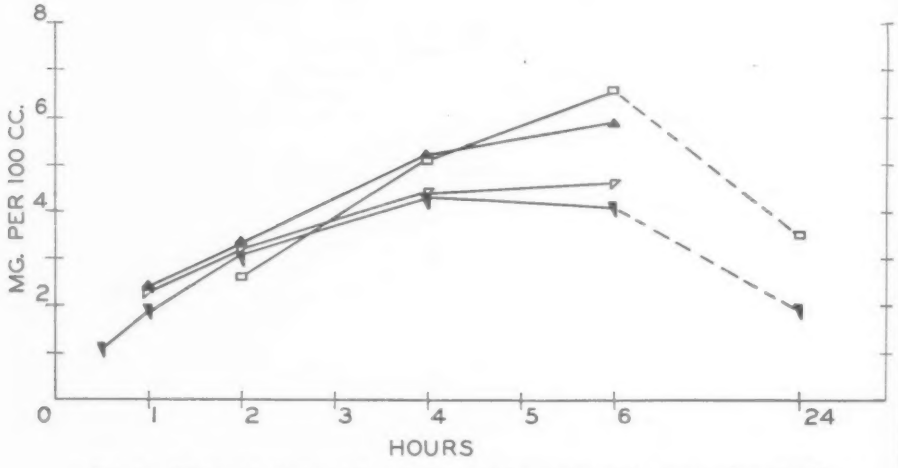

FIG. 3.—Effect of fasting and flavoring material, together with a comparison of tablets and suspensions of sulfadiazine on sulfadiazine concentrations in serum. Rectangles: sulfadiazine tablets, non-fasting, 9 subjects. Solid upright triangles: sulfadiazine suspension, non-fasting, 8 subjects. Open triangles: sulfadiazine suspension with added sucrose, fasting, 6 subjects. Solid inverted triangles: sulfadiazine suspension with added sucrose, non-fasting, 7 subjects.

It will be seen that the standard errors (Fig. 4) of the averaged urine excretions were much smaller in the group receiving microcrystalline preparations than in those receiving plain sulfadiazine. Likewise, there was less variation in the individual serum sulfadiazine curves when microcrystalline preparations were ingested. This more uniform response when microcrystals were administered was a consistent finding. The same individuals to a predominant extent made up the two groups; thus individual differences were not the cause.

Forty-five patients receiving microcrystalline preparations (4 gm. per day at 6 hour intervals) for periods up to 10 days showed an average sulfadiazine concentration of 9.3 mg. per 100 cc. serum. An entirely comparable group of 45 receiving sulfadiazine in the same amount, either as tablets or as a suspension in sucrose solution with other flavoring material, yielded an average of 10 mg. per 100 cc. The difference is not statistically significant.

Observation of the therapeutic action of microcrystalline sulfadiazine in 75 patients suffering from pneumonia showed no evidence of decreased therapeutic effectiveness or of increased toxicity, as compared with ordinary sulfadiazine.[3]

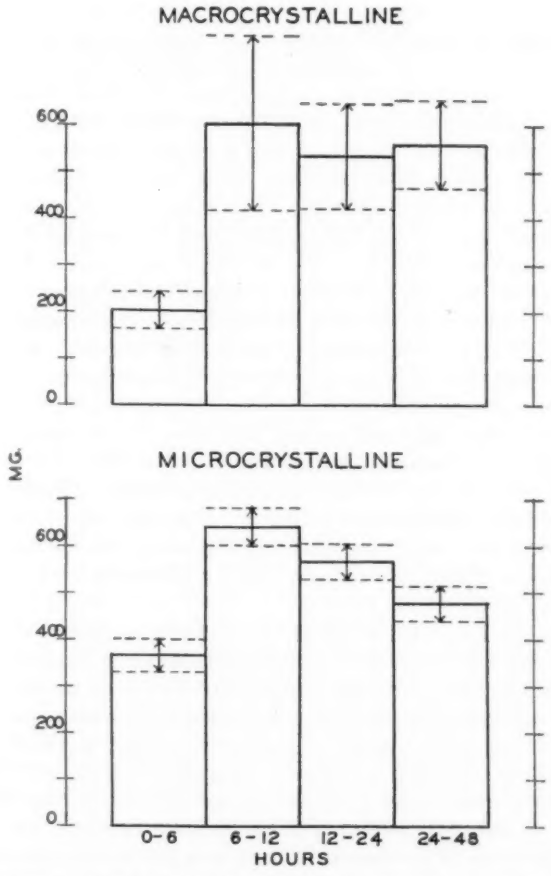

FIG. 4.—Excretion of sulfadiazine in urine after ingestion of microcrystalline preparations compared with ordinary sulfadiazine preparations. The dotted lines and arrows show the standard errors of the means.

Discussion. The more rapid rise in concentrations of sulfadiazine in serum and the more rapid excretion in urine during the 1st hours following ingestion of microcrystalline sulfadiazine must be the result of an increased rate of absorption when in this form. The most plausible explanation is that microcrystalline material remains in suspension in the stomach and consequently is moved toward the pylorus and discharged into the duodenum sooner than is ordinary sulfadiazine. The latter settled from suspensions in water rapidly and thus could easily deposit in the body of the stomach, with the result that its

movement toward the pyloric antrum would be delayed. Suspensions of ordinary crystals in sucrose were more permanent but their effect was negligible, again because dilution of the sucrose in the stomach would permit precipitation.

Accelerated absorption of microcrystalline sulfadiazine when the stomach contains food probably is the result of increased peristaltic activity causing more rapid movement of the suspended material into the pylorus. Absence of a similar effect of food when ordinary crystals are ingested would likewise be the result of failure of such crystals to remain suspended as the contents of the stomach became liquefied. It should be noted that Peterson and Finland[7] observed higher concentrations of sulfadiazine in blood when their subjects had eaten breakfast than in fasting subjects. The difference observed was quite similar to that seen in the group described by us who had ingested microcrystalline sulfadiazine. We failed to find any indication of a similar effect in our subjects when ordinary sulfadiazine was investigated. No evidence exists that absorption of sulfadiazine occurs in the stomach. Even if it were physiologically feasible, the solubility in acid solutions is so very low as to preclude any appreciable contribution to the serum sulfadiazine concentration from this source.

Another possible explanation for the more rapid uptake of sulfadiazine in microcrystalline form is a difference in rate of solution when in contact with alkaline secretions in the intestine. However, experiments in which sulfadiazine, either in ordinary or microcrystalline form, was exposed briefly to solutions of sodium bicarbonate at pH 8 failed to show a difference between the two with respect to the amount dissolved.

Summary 1. Patients receiving by mouth suspensions of microcrystalline sulfadiazine (3 gm.) showed significantly higher concentrations of sulfadiazine in serum during the first 6 hours following its ingestion than did those who received ordinary sulfadiazine.

2. The excretion of sulfadiazine in the urine of those receiving microcrystalline material was likewise significantly higher during this period. These observations indicate that microcrystalline sulfadiazine is absorbed more rapidly than is ordinary sulfadiazine.

3. The presence of sucrose or of flavoring material had no influence on the rate of absorption of microcrystalline sulfadiazine or ordinary sulfadiazine.

4. In fasting subjects, the rate of absorption of microcrystalline sulfadiazine was decreased, but remained greater than that of ordinary sulfadiazine whether fasting or after meals. No such effect of fasting was observed in subjects given ordinary sulfadiazine.

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PENICILLIN—ITS PRESENT STATUS IN THE TREATMENT OF INFECTIONS*

The Nathan Hatfield Lecture XXIX

By Chester S. Keefer
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Several weeks ago, a young woman was admitted to our Clinic at the Evans Memorial complaining of chills and fever. She had been well until 3 days before admission when there was a sudden departure of health. Upon examination, it was found that she had high fever, pain in the right ankle joint, and the physical signs of a bilateral bronchopneumonia. The blood culture showed numerous colonies of *Staphylococcus aureus*. She was placed on penicillin therapy at once. Within the first 2 days the temperature was reduced to a lower level, but she developed a right-sided hemiparesis with aphasia, and the signs of an acute arthritis of the right ankle joint. Gradually over a period of 3 weeks the temperature returned to normal, the other signs of infection disappeared and she made a complete recovery with the exception of a slight weakness of the right arm. The course of this patient's illness illustrates what can be accomplished in 90% of all cases of *S. aureus* infections with bacteremias when penicillin is given in adequate amounts for a sufficiently long period of time. When one recalls that the fatality rate in this disorder is usually between 50% and 75% without penicillin, it is plain that penicillin has completely changed the outlook in this group of infections. But this is not all. It can be said without reservation that penicillin is the most remarkable chemotherapeutic agent that has been discovered up to the present time. When one makes such a statement it is well to document it. In the first place, it is a substance of extremely great antibacterial power. One mg. of crystalline penicillin is capable of inhibiting the growth of staphylococci in 82.5 liters of broth. It is non-toxic in maximum therapeutic doses in man. It is highly effective against a wide variety of microörganisms of the gram-positive group. It is effective in both gonorrhea and syphilis, the two commonest genito-infectious diseases. It is responsible for the reduction of the fatality rate in more diseases than any other chemotherapeutic agent; it

* The work in preparing this review was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Memorial Hospitals, Robert Dawson Evans Memorial, Department of Clinical Research and Preventive Medicine.

shortens the clinical course of many infectious disorders, and it saves many days of illness and disability. When one realizes that this can be accomplished by an agent that destroys bacteria and other microorganisms such as the *Treponema pallidum* without injuring the tissues of the host, it deserves to be called remarkable. No other known agent can do as much.

There are many fascinating historical events to be recorded in the development of penicillin. At this time 3 years ago, there was not enough penicillin in this country to treat a single patient. Two years ago, only 100 patients had received treatment. Today there is enough penicillin being produced in this country alone to supply our Armed Services and those of our Allies, and a moderate amount for civilians. This progress has been due to the combined efforts of many groups working in universities, hospitals, in industry and in government.

Tonight I want to review for you the present status of penicillin treatment in the common infections.

Salts Used and Routes of Administration. First of all, I shall make a few remarks concerning the best route of administration. There are 2 salts of penicillin available for clinical use, the sodium and the calcium salts. They are both equally effective therapeutically and they can both be used interchangeably. The commonest route of administration is the intramuscular, and it is the route of choice. Injections may be given intermittently or continuously. It may also be given intravenously, and topically into the serous cavities, joint cavities, or into the subarachnoid space.

In an attempt to delay absorption from local deposits in the muscles, penicillin has been combined with beeswax and peanut oil or with gelatin and vasoconstrictor drugs. These methods show considerable promise and when the details have been worked out, the use of such a method will undoubtedly reduce the number of injections required to maintain adequate concentrations of penicillin in the blood and tissues.

When penicillin is given by mouth, the coefficient of absorption is small and varies between 2 and 10%. When large amounts are given by this route and at frequent intervals in oil, or in buffers such as sodium citrate, a sufficient amount is absorbed to influence the course of infections. In the case of gonorrhea or lobar pneumonia, recovery may be observed following the use of 5 to 10 times as much as is needed when penicillin is given parenterally. At present the use of penicillin by mouth is wasteful, uncertain and expensive, when compared to other routes of administration.

Dosage. It is difficult, and indeed impossible, to make any absolute rules concerning the necessary dosage of penicillin that will be universally applicable. The daily and total dose will depend upon the type of infection, its location, the presence of bacteremia, the age and the clinical condition of the patient and the course of the disease.

For example, it is a well-established fact that there is a wide variation in the susceptibility of various organisms to penicillin. The gonococcus is the most sensitive organism so that between 50,000 and

150,000 units will cure 98% of cases of gonorrhea within 24 hours. The hemolytic *Staphylococcus aureus* is more resistant, so that between 100,000 and 200,000 units a day for 1 to 3 weeks or longer may be required. In the case of bacterial endocarditis due to *Streptococcus viridans*, at least 300,000 units daily for a period of 14 to 21 days may be considered a minimum dose.

One of the greatest difficulties in assessing dosage is the lack of signs of toxicity so that the maximum tolerated dose is not known. Conversely the minimum effect dose is difficult to define in all cases. The most reliable guides to dosage are the type of specific organism and the response of the patient to treatment.

Generalized Infections With Bacteremia. Generalized infections with bacteremia due to susceptible organisms, such as the *S. aureus*, *Strep. hemolyticus* or the pneumococcus, respond in a most favorable manner to penicillin. The outlook in individual cases will depend to some extent upon such factors as the source of the primary infection, the age of the patient, the period at which treatment is begun and, in some instances, the accessibility of the infection to surgical treatment. The best results have been obtained in young individuals who have a recent infection and who have been given active and intensive treatment with 120,000 to 240,000 units a day. Less favorable results have been seen in elderly patients with overwhelming infections, bacterial endocarditis, meningitis, or when the infection is associated with some complicating debilitating disease.

In the case of staphylococcic bacteremia, the overall fatality rate has been reduced to within 10 to 20%. It has been lowest in young persons with osteomyelitis (10%) and highest in those with bacterial endocarditis (75%).

In all cases with bacteremia the treatment should be continuous for 2 to 3 weeks and enough penicillin should be given daily to bring the infection under control.

Infections of the Meninges. *Meningococcus Meningitis.* Sulfadiazine continues to be the drug of choice in the treatment of meningococcic meningitis. While penicillin is effective in controlling this disease, the response is slower than following the sulfonamides, and it continues to be necessary to give penicillin both systemically and intrathecally. In cases failing to respond to the sulfonamides within a period of 24 to 48 hours with adequate treatment, penicillin should be started at once. Penicillin is the drug of choice in the treatment of all infections of the meninges due to the pneumococcus, staphylococcus and the hemolytic streptococcus. Treatment should be started as soon as the diagnosis is established, and all foci of infection in the neighborhood which can be drained surgically should be attacked at the same time. This is especially true when there is an associated mastoiditis or lateral sinus thrombosis.

Pneumococcus Meningitis. Pneumococcus meningitis is always a serious disease. Before the days of the sulfonamides it was invariably fatal. Now a certain number of patients, that is, between 40 and 50%, recover following the use of either the sulfonamides or penicillin.

There is some evidence that the combination of sulfadiazine and penicillin may be better than either drug alone.[1]

One of the reasons that pneumococcus meningitis is such a serious disease is that it is frequently a metastatic lesion following pneumococcus lobar pneumonia with or without an associated bacterial endocarditis. In other cases it follows craniocerebral injuries, otitis media and/or mastoiditis or suppurative sinusitis of the ethmoid or sphenoid cells. Another reason for the severity of this infection is that it tends to produce hydrocephalus and an encephalitis which may lead to cerebral atrophy and profound neuropsychiatric disturbances.

Otitis Media and Mastoiditis. Patients with otitis media and mastoiditis respond to penicillin treatment most favorably. In the case of mastoiditis, simple mastoidectomy followed by closure of the incision with the insertion of a small catheter so that penicillin can be instilled into the cavity for 3 or 4 days is the method of choice, as demonstrated by Johnson, Weinstein and Spence.[2] Under these conditions healing takes place rapidly and the postoperative course is greatly shortened.

Tonsillitis. Tonsillitis resulting from hemolytic streptococcal infection responds very promptly to the use of penicillin. Treatment should be continued for at least 5 to 7 days in order to prevent relapses. One of the striking features following the treatment is the rapid decrease in the number of organisms in the throat. Indeed, it is often difficult to recover streptococci from the local focus of infection 24 or 48 hours after treatment is started. If, however, there is an interruption of treatment, there may be relapses of infection and organisms will reappear in great numbers in the throat. For this reason, it is essential that the treatment be continued for at least several days after all signs of acute infection have subsided.

Pneumococcus Pneumonia. The pneumococcus is extremely susceptible to the action of penicillin *in vitro* and when patients with pneumococcus lobar pneumonia receive penicillin, the outcome is extremely favorable. Tillett, Cambier and McCormack[3] have recorded a fatality rate of only 6.5% in 106 cases, and in all of the fatal cases there were complicating factors. Meads, Harris and Finland[4] record favorable results in cases in which the sulfonamides had previously failed to control the infection. The latter group of investigators found that penicillin was equally effective in the patients who had received it alone or in those who had failed to respond to the sulfonamides.

There are a number of points worth commenting on with respect to the treatment of pneumococcus lobar pneumonia with penicillin. When patients are treated early in the course of their disease, that is, within the first 24 or 48 hours, there is usually a decrease in the temperature and pulse rate within the first 24 to 48 hours and preceding these objective signs, the patients feel improved subjectively.

Bacteremia, if present, disappears promptly, usually following the first injection, and purulent complications following the use of penicillin are exceedingly uncommon. They were not observed by Meads, Harris and Finland in any of their cases.

The dosage and duration of treatment will vary from one patient to

another, depending upon the clinical response and the severity of the infection. In some mild cases, a satisfactory response has been observed following 60,000 to 80,000 units a day for 2 days, given in doses of 10,000 units every 3 or 4 hours. In other cases, the equivalent of at least 15,000 units every 2 hours for the first 12 or 24 hours, after which longer intervals or smaller amounts may be used for another 2 or 3 days. It is wise and sound practice to continue treatment for 2 or 3 days after the temperature has reached normal in order to avoid relapses which may be observed if treatment is stopped abruptly after the first 48 or 72 hours. Certainly the total dosage during the first 24 hours must be gauged by the condition of the patient and his response to the treatment.

In attempting to assess the conditions in which the sulfonamides or penicillin should be used in the treatment of pneumococcus lobar pneumonia, it is not possible at the time of this writing to make any definitive rules. Both agents are effective. However, the sulfonamides can be given by mouth and penicillin must be given parenterally. This may be a consideration in some cases. However, it is well to recall that penicillin is non-toxic and that the sulfonamides may cause side reactions. In general, it can be said that penicillin is the drug of choice in: (1) all patients who have failed to respond to the sulfonamides after 24 hours of treatment; (2) all patients with a persistent bacteremia; (3) all patients who show a spread of the process; (4) all patients who develop any signs of sulfonamide intoxication or renal irritation; and (5) all patients who have leukopenia or who develop auricular fibrillation, delirium tremens or other complications during the infection.

It is well to start with penicillin when the patient is acutely ill or has developed a shock-like state, or when he has some complicating disease such as renal, hepatic, or cardiac disorder, or when there is leukopenia or a history of sensitivity to the sulfonamides.

In brief, it can be said that penicillin can be given with greater safety than sulfadiazine and with the same good results. It will gradually become the drug of choice in the treatment of all cases of pneumonia.

Subacute Bacterial Endocarditis. When subacute bacterial endocarditis due to the non-hemolytic streptococcus was first studied, the results of penicillin treatment on the clinical course were discouraging. In some cases, when 30,000 to 60,000 units were given daily, the blood was cleared of organisms and the temperature was reduced for the period of treatment. However, the course of the disease was not otherwise influenced and when the drug was withdrawn, the bacteremia recurred and progressive signs of infection ensued. It is now known that these results were due to an inadequate amount of penicillin. When larger amounts of penicillin are given for longer periods of time, that is, 200,000 or 300,000 units a day for at least 3 weeks, there will be a clinical arrest of the disease varying from 1 to 10 months in about 55% of cases (Fig. 1). A certain number of patients will die before adequate treatment as described above has been completed. Death

in these cases is due to the infection, to embolism or to acute heart failure.

When clinical arrest takes place, the following sequence of events may be observed. Within 24 to 72 hours after treatment is started, the patients often lose many of the constitutional symptoms of infection. The anorexia disappears, the appetite improves, and the patient becomes more interested in his surroundings. The temperature is promptly reduced in some cases to within normal limits within the 1st week. In others, after the initial decrease in temperature, the fever may continue for a 6- to 8-week period as low grade fever. In a third group, it may go down only after 2 to 3 weeks. Prolonged fever after beginning treatment may be due to an infection by a relatively resistant organism, or it may be due to a complication or a continuing tissue reaction. Once the temperature becomes normal, there may be occasional recurrences due to embolic phenomena.

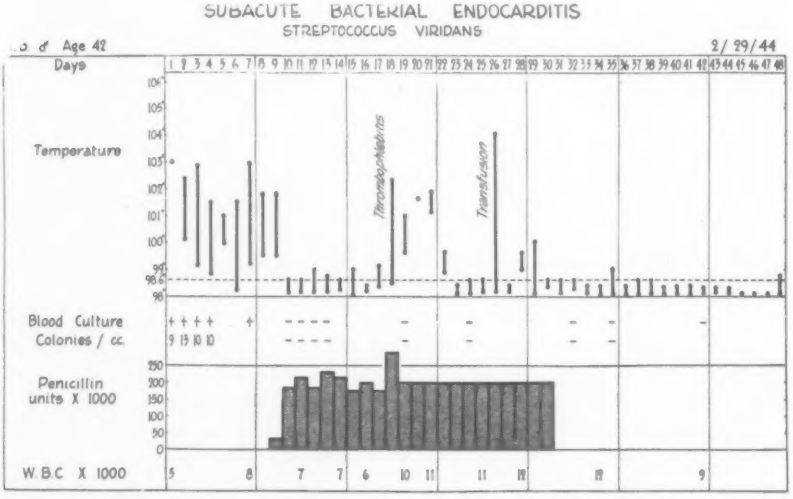

FIG. 1.—The clinical arrest of a patient with subacute bacterial endocarditis. The blood was promptly cleared of organisms; the temperature returned to normal within 72 hours after penicillin was begun. Thrombophlebitis and blood transfusions were followed by fever.

Within 1 to 5 days after treatment, the blood cultures generally become negative and remain so except for occasional instances when a transitory bacteremia and embolic phenomena occur.

Petechial hemorrhages may continue to occur for 6 to 8 weeks after treatment is started and emboli may occur up to 2 months. The spleen decreases in size, the leukocytes decrease in number, anemia improves, clubbing of the fingers may recede.

As might be anticipated, there are no changes in the signs of valvular disease and the renal lesions are not favorably influenced by treatment. It is now well established that all of these favorable results may be

obtained with penicillin alone and no anticoagulant such as heparin is necessary.

Following a clinical arrest, the patient may return to apparently normal health in that the symptoms and signs of infection are absent. Some patients have recurrences as long as 6 to 9 months after treatment. A number of patients die of cardiac insufficiency without signs of active infection.

Acute Osteomyelitis. Evidence is now accumulating that acute osteomyelitis can be treated satisfactorily without surgical intervention when the therapy is started early in the course of the disease and before abscesses of the soft parts or extension of the infections of the joints has occurred. Penicillin must be given in amounts varying from 120,000 to 250,000 units a day and continued for a period of 2 to 3 weeks until all clinical symptoms and signs of infection have disappeared. Since there is a lag between the clinical signs of infection and the development of definite roentgenologic changes in the bone, one is not surprised to find that destruction of the bone is observed some time after all signs of infection have disappeared. Under these conditions, the lesions in the bone frequently recalcify and complete healing takes place without incision and drainage.

When the infection has spread into a neighboring joint, it is desirable to perform whatever surgery is necessary to make possible the local instillation of penicillin into the involved joint at least once or twice a day. In all cases of acute osteomyelitis in which recovery has taken place without surgical treatment, the patient should be followed carefully over a period of several months in order to be certain that relapses or recurrences do not occur. In a few cases it may be necessary to drain local abscesses in bone some weeks after the acute infection has subsided. In occasional cases that have been treated very early, no signs of bone destruction have ever developed in the roentgenograms.

The treatment of osteomyelitis of the facial bones with penicillin has been followed by excellent results, as reported by Kirby and Hepp.[5] When sequestra were present, surgical treatment in addition to the use of penicillin was necessary to effect complete recovery.

In the case of chronic, hematogenous and traumatic osteomyelitis, Anderson, Howard and Rammelkamp[6] have found that when sequestra are present it is necessary to remove them surgically in order to obtain satisfactory healing. These physicians were able to report an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70% of their patients with chronic osteomyelitis. Prolonged treatment varying from 2 to 6 weeks was found to be necessary in order to obtain the best results. Treatment has to be repeated when relapses occur. Primary closure of wounds after sequestrectomy, together with the local administration of penicillin, greatly shortens the recovery period. In brief, the treatment of acute and chronic osteomyelitis should be designed to control the infection as rapidly as possible. If dead or necrotic tissue is present, or if abscesses in the soft parts or in the joints have appeared, it is necessary

to use good surgical management as well as penicillin if the best results are to be obtained.

Infections Due to Clostridia. *Gas Gangrene.* The best results in the treatment of gas gangrene follow the use of antitoxin, penicillin, and surgical removal of all necrotic and damaged tissue. If gas gangrene tends to develop in patients who have had injuries to the bone and soft parts with an interruption of the blood supply to the affected part, it is only natural that a certain number of patients will not respond to any form of treatment unless all of the ischemic and damaged tissue has been removed. Jeffrey and Thomson,[7] in a study of 33 cases of gas gangrene treated with penicillin, reported a fatality rate of 36.4%. They emphasize, as has already been remarked, that adequate surgical removal of all necrotic and devitalized tissue is the most essential of therapeutic procedures in the management of gas gangrene. Five of their patients were seen late in the disease when surgical treatment was not possible. All of these patients died in spite of intensive treatment with penicillin. These physicians recommend a dosage of 15,000 units every 3 hours for 3 to 4 days for the control of infection in cases in which all the infected tissue can be removed surgically. When this is not possible, it is desirable to continue treatment for 5 to 10 days. They express the opinion that when patients are treated early and adequate surgery is employed, penicillin and antitoxin will reduce the fatality rate in battle casualties to the neighborhood of 20%. Cutler and Sandusky[8] reported their experience with the treatment of 7 patients with gas gangrene, 6 of whom recovered. It is significant that in 5 of their patients, gas gangrene developed while the patients were receiving prophylactic penicillin therapy. Following the removal of diseased tissue, all of these patients recovered.

Gonococcic Infections. Of all the organisms that are susceptible to penicillin, the gonococcus is the most sensitive. It is now well established that about 98% of all gonococcic infections of the lower genital tract, either in men or women, can be cured by the administration of a total of 100,000 units of penicillin over a 24-hour period. The remaining 2% who fail to respond to the first course frequently respond to more intensive and prolonged treatment. No proved cases of penicillin-resistant gonorrhea have yet been encountered.

Gonococcic infections complicated by arthritis, prostatitis, salpingitis, epididymitis, or endocarditis, require much more prolonged treatment. Early and intensive treatment in all of these infections is advisable.

Syphilis. Following the report of Mahoney and his associates[9] in October 1943, intensive studies of the treatment of early syphilis, neurosyphilis and congenital syphilis have been carried out by a group of coöperating clinics reporting to the Penicillin Panel of the Subcommittee on Venereal Diseases of the National Research Council, and coöperating with the Committee on Medical Research of the Office of Scientific Research and Development. Final evaluation of the results will, of course, not be possible for several years. Preliminary reports indicate that a course of 60 injections of 20,000 units each,

given intramuscularly at 3-hour intervals for 7½ days, probably represents the minimum dosage schedule that will be effective in controlling primary and secondary syphilis. In some patients who relapse after this schedule of treatment, more prolonged and intensive treatment may be necessary. Not enough time has elapsed, and too few patients with neurosyphilis have been treated for a sufficiently long period of time to make any statement concerning the results that might be anticipated. There is some evidence to suggest that the results in the treatment of neurosyphilis are not as striking as those of early syphilis. Late cutaneous and osseous syphilis apparently respond promptly to penicillin treatment. So far, no reports are available on the action of penicillin in latent syphilis. Some cases of congenital syphilis have been treated in which good early results have been obtained.[10] It is agreed by all who are investigating this problem, that penicillin in the treatment of syphilis is still in the stage of preliminary investigation, and no definite schedule of treatment can yet be recommended for routine therapy.

During the treatment of syphilis with penicillin, Herxheimer reactions have occurred with considerable frequency. These are characterized by fever, malaise, headache, intensification of the eruption if one is present, or painful swelling of the primary lesions and the regional lymph nodes. These reactions subside within 24 hours and are not contraindications to continuing treatment.

Toxic Reactions. It has already been stated that penicillin is a nontoxic drug. There are, however, certain side reactions which may be observed which require comment. So far, no permanent harmful effects on any of the systems of the body have been recorded.

About 2 to 5% of patients develop *urticaria*. The urticaria may appear on the 1st day of treatment, or it may not appear until after treatment has been completed. When it develops, it is commonly seen during the 2nd week of treatment. In a few instances it may be quite severe and extensive, but in most cases it is mild and frequently disappears even though treatment is continued. When penicillin is readministered at a later date to a patient who has developed urticaria during the previous course of treatment, there may be a reappearance of the eruption. Urticaria is not regarded as a contraindication to continuing treatment or to readministration of the drug at a later date in most cases. In rare instances it may be advisable to stop treatment, especially if the discomfort is severe.

Occasional attacks of *vesicular eruptions* have been noted and we have seen one severe rash of this type appearing within 24 hours after the beginning of treatment, especially in areas where there was a severe ringworm infection 4 years previously.

Pain on intramuscular injection is encountered with varying frequency, depending upon the presence of impurities in the penicillin. The higher the potency of the penicillin, the less local discomfort there may be.

Thrombophlebitis of the veins at the site of injection may occur, especially in patients who are receiving continuous intravenous treat-

ment. Thrombophlebitis is associated in some instances with chills and high fever. When this occurs, it is wise to change from intravenous to intramuscular injections. All preparations of penicillin which are now distributed are tested for the presence of pyrogenic agents. The febrile reactions due to impurities that were occasionally encountered in the early days of developing penicillin are no longer seen. Drug fever, analogous to that seen in sulfonamide therapy, has not been reported. Occasionally patients may develop low grade fever after the clinical signs of infection have disappeared, and this subsides completely with the discontinuance of penicillin.

Occasional patients will develop *abdominal cramps* with or without *diarrhea* following penicillin, and *nausea* and *vomiting* have been observed in a few patients. The maximum therapeutic dose of penicillin that can be given safely in man has not yet been determined. It is known that doses as large as 4 million units a day have been given in 1 or 2 instances without ill-effect.

At present there are no known contraindications to the administration of penicillin, although there may be reason for giving small initial doses to patients with cardiovascular extragenital syphilis. As far as is known, penicillin is not incompatible with any other drug or article of diet.

Miscellaneous Infections. A large group of miscellaneous infections have received treatment with penicillin with promising results. In most instances the number of cases so treated has not been large, so that final assessment of its value cannot be made. However, patients with *actinomycosis* have been improved following treatment, and especially those cases in which it is possible to remove infected tissue surgically, or in those instances in which there is a superinfection due to the *S. aureus*. *Anthrax*, with or without bacteremia, responds promptly to penicillin, and a few cases of yaws and rat-bite fever due to *Streptobacillus moniliformis* have been treated with results suggesting that penicillin is a potent agent in these disorders.

Penicillin is active *in vitro* against *Corynebacterium diphtheriæ;* a few cases of clinical diphtheria have been treated with a combination of antitoxin and penicillin with results that are difficult to evaluate. Penicillin will not replace antitoxin and should not be used *in lieu* of antitoxin. The supplementing of antitoxin with penicillin in cases of laryngeal diphtheria or diphtheria gravis may prove to be valuable, although the evidence to support this procedure remains to be accumulated. The treatment of diphtheria carriers with penicillin has not met with permanent success.

The position of penicillin in the treatment of chronic paranasal sinusitis, chronic infections of the ears, nose and throat, remains to be determined. The same is true with gingivitis and stomatitis caused by the Vincent organism.

Prophylactic Use of Penicillin. White and associates[11] have demonstrated that when penicillin is administered intramuscularly for 1 week prior to lobectomy or pneumonectomy and followed by continuation of penicillin treatment after operation, the incidence of postoperative

empyema is greatly reduced. Penicillin will perhaps not decrease the number of infections in wounds when it is not combined with adequate surgical treatment.

Penicillin Failures. No discussion of penicillin would be complete without saying something about the cases in which penicillin fails to influence the course of the disease. The largest group, of course, includes those cases of infection due to microörganisms which are not susceptible to the action of penicillin such as those listed in Table 1:

TABLE 1

Typhoid—paratyphoid	*B. pyocyaneus*
Dysentery (several varieties)	*Br. melitensis* (undulant fever)
E. coli	*P. tularense* (tularemia)
H. influenza	*B. friedländer*
B. proteus	

The next large group are those disorders in which penicillin has been shown to be ineffective as listed in Table 2:

TABLE II

Tuberculosis	Pemphigus
Poliomyelitis	Toxoplasmosis
Hodgkin's disease	Blastomycosis
Histoplasmosis	Coccidiomycosis
Moniliasis	Acute rheumatic fever
Malaria	Virus infections
Cancer	Acute and chronic leukemia
Lupus erythematosus, diffuse	Ulcerative colitis
Non-specific iritis and uveitis	Infectious mononucleosis

In general it can be said that there is a fairly good correlation between the sensitivity of the infecting strain of microörganism and the clinical amenability to treatment, so that when the treatment appears to fail it may be due to inadequate daily dosage or to treatment of only a few days duration. The treatment may be started too late in the course of an infection, or there may be an overwhelming infection even with a sensitive strain.

In the case of wound infections, penicillin may fail in its function when débridement is incomplete, or when necrotic tissue or foreign bodies are present.

In our experience the development of increased resistance of microorganisms to penicillin plays little if any rôle in the failure of infections to respond to its action. While we can demonstrate a change of sensitivity in some strains of *S. aureus* during treatment when they are tested *in vitro*, the evidence is far from convincing that this phenomenon plays a dominant rôle when a regression of signs of infection fails to occur. The reason for this statement is that there are usually other factors present which influence the outcome. This is especially true when the resistance to penicillin increases in organisms in empyema cavities and in chronic osteomyelitis.

In brief, when any patient with an infection due to a susceptible organism fails to show a satisfactory response to penicillin, one should review the dosage, search for signs of a bacterial endocarditis, or an abscess which has not been drained.

Conclusion. In conclusion, it can be said that penicillin has exceeded our highest hopes as a chemotherapeutic agent. It is unquestionably the most effective agent for the treatment of many infections. There is no other known chemical that is so powerful against bacteria and so harmless to the host.

All of this is most extraordinary when one appreciates that 50 mg. will cure the average gonococcic infection, 300 mg. or less is needed for patients with pneumococcus lobar pneumonia, and 3 to 5 gm. will arrest between 50 and 70% of the infections in subacute bacterial endocarditis.

What we need in the future are effective agents for the similar control of gram-negative bacillary infections and virus infections.

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A STUDY OF THE TYPES OF HYPERSENSITIVITY INDUCED BY PENICILLIN*

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Following the finding[7] of a case of hypersensitivity of the tuberculin type to crystalline penicillin sodium in an individual who had had no previous contact with this drug, a study was made to determine

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the incidence of this type of sensitivity. Studies were made also of the sensitivity induced by the injection of commercial or crystalline penicillin sodium.

To determine the incidence of the tuberculin type of sensitivity to penicillin 144 persons were tested. Each was injected intradermally in the volar surface of the forearm with 0.1 cc. of penicillin sodium containing 1000 units. In all cases where a positive reaction resulted, a retest was made with crystalline penicillin. Of the 144 individuals tested, 106 were healthy inmates of a penal institution, 27 were laboratory personnel, and 11 were employees of manufacturing plants producing penicillin. Eight individuals (5.5%) exhibited hypersensitivity of the tuberculin type when tested initially. Attempts to show a passive transfer of the hypersensitivity using the Prausnitz-Küstner technique and the Urbach-Koenigstein[6] method both failed. (The latter method was attempted with the blister fluid from 5 positives and as many recipients were used.*)

It had been noted previously[7] that following intradermal injection of commercial penicillin in man there developed a "flaring" phenomenon in certain persons which appeared only after a variable number of injections had been made. This phenomenon consisted of an increase in redness and itching at sites of former injections, following the intradermal injection of crystalline penicillin sodium in a new site. It was also noted that the persons who had exhibited this type of reaction failed to do so after a rest period during which no injections were made. It was decided to study this phenomenon further in view of the fact that these original observations were a by-product of other studies, and consequently the persons manifesting them had not had the same number of injections or the same spacing between injections. Nine individuals were injected intradermally in the volar surface of the lower right arm with 10,000 units of commercial penicillin sodium, 1000 units in 0.05 cc. of saline at each of 10 different sites. These injections were repeated in approximately the same areas 5 days and 10 days later, a total of 30 injections. The material used was commercial penicillin, the products of 7 manufacturers. Following the first series of 10 injections some of the subjects showed evidences of chemical irritation at some of the sites; all who showed the irritation developed it from the same lots of penicillin. Following the second series of 10 intradermal injections reactions occurred in 2 of the people. One individual who had previously received intradermal injections of penicillin showed at the sites of old injections the flaring phenomenon already described. Another developed urticaria approximately 30 hours after injection. The wheals were diffusely distributed, the face and eyelids were swollen, and swelling of the fingers and hands was

* In order to exclude the possibility that the consistently negative P–K tests were the result of an accidental selection of test subjects incapable of accepting passive transference reagins, serum from a ragweed-sensitive person was also used. At the time the recipients were tested with penicillin they were also tested with a ragweed pollen extract. In all cases positive transference was readily demonstrated with the serum of a ragweed-sensitive person. In the case of the U–K test blisters were raised by means of a cantharides cerate over sites of recently reacting penicillin areas.

pronounced. The individual showed dermatographia, lacrimation and conjunctival injection. The reactions occurred in waves approximately every hour or 2 during the first 4 days but did not stop entirely until 7 days had elapsed. Two days after the reaction had subsided an attempt was made to transfer her sensitivity to 3 normal individuals by the Prausnitz-Küstner technique. Passive transfer was not successful. In view of her general reaction she was tested to determine whether she would exhibit an immediate wheal reaction to the intradermal injection of crystalline penicillin. To avoid a possible systemic reaction, only 50 units of crystalline penicillin sodium were used in the initial test. This was dissolved in 0.02 cc. of saline, injected intradermally in the volar surface of the forearm and the site observed for about 15 minutes. There was no evidence of a reaction. An intradermal test was then made with 200 units of crystalline penicillin in the same manner. A control injection of 0.02 cc. of isotonic saline was made simultaneously. Within 5 to 10 minutes there was a moderate-sized erythematous halo about the site where the crystalline penicillin had been injected and the wheal formed by the introduction of the fluid increased slightly in size. This was considered to be a weakly positive urticarial type of reaction. In contrast to this, the wheal produced by the control injection decreased in size. Another attempt was made, 2 weeks after this this individual recovered, to transfer passively her sensitivity to 4 normal individuals by means of the P–K technique. Again it was found impossible to demonstrate passive transference. Precipitin tests done on 2 occasions on this person's serum were questionable.

For the third series of 10 intradermal injections, 8 persons were used. The reactions following these injections varied considerably. Four of the test subjects showed within 15 to 30 minutes erythema around all injected sites; in some the erythema became confluent (Figs. 1 and 2), and persisted for at least 24 hours. Wheals, varying in size from 5 to 15 mm., developed in 2 of these individuals and then subsided within from 1 to 2 hours. (Fig. 2 shows the wheals well.) The other 4 test subjects showed, in addition to whealing and marked erythema at the sites of injection, the "flaring" reaction at old sites of injection (Fig. 3). One of the latter group of 4 individuals exhibited the most intense reactions. This person received only 4 injections in the third series instead of 10 because he had exhibited a strong flaring reaction following the second series of injections. Within 15 minutes after the third series of injections he showed marked erythema and slight wheals which persisted for only from 1 to 2 hours. Eighteen hours later, at the site of the last 4 injections, erythematous areas redeveloped approximately 30 mm. in diameter and there was marked flaring at all previous sites of injection (Fig. 4). At approximately the 24th hour the 4 sites injected in the third series showed red areas about 25 mm. in diameter surrounded by a narrow, white, non-erythematous zone outside of which was a 3 mm. zone of erythema concentric with the inner one (Fig. 5). The old sites of injection were still flaring at the 30th hour.

FIG. 1

FIG. 2

FIGS. 1 and 2.—Development of diffuse erythema and wheals following intradermal injection of penicillin sodium.

FIG. 3.—"Flaring" of old sites (*A*) following injection of new sites (*B*).

FIG. 4.—Marked erythema and "flaring" reaction at old sites 18 hours after intradermal injection of penicillin sodium at four sites marked "A".

It was decided to attempt to induce sensitivity by varying the technique of administration. Three routes of injection were used. In the first group 10 individuals were given 30 intradermal injections of 1000 units each of commercial penicillin sodium, and 3 individuals were given a similar number of injections of crystalline material, in exactly the same manner as those recorded above, except that the time elapsing between each series of 10 injections was 48 hours instead of 5 days. A second group of 10 individuals was injected subcutaneously, each with 30,000 units of penicillin sodium given in 3 doses of 10,000 units each, 48 hours apart. Finally, a third group of 10 individuals was

FIG. 5.—Tuberculin type reactions with zones of desensitization (sites marked "A") 24 hours after intradermal injection of penicillin sodium.

injected every 48 hours with 10,000 units of penicillin sodium (5000 units intravenously and 5000 units subcutaneously) until 30,000 units per person had been given.

Only 1 person developed an increase in sensitivity, and this individual was one of those injected intradermally with crystalline penicillin sodium. This person, 24 hours after the third series of injections, showed small-sized tuberculin type reactions at the sites of the injections. Intradermal tests were done with crystalline penicillin on all persons in all groups 48 hours and 1 week after the last injection. All of these tests were negative.

Two individuals not included in the above series had previously shown flaring following the intradermal injection of small amounts of

commercial penicillin sodium. In order to determine whether these persons would still exhibit this phenomenon they were injected in the volar surface of the forearm with 1000 units of crystalline penicillin sodium in 0.05 cc. of saline. No flaring occurred in either individual. It appeared, therefore, that their previous exhibition of flaring was a transient phenomenon. In an effort to reëstablish the flaring phenomenon both were given 10 intradermal injections in the volar surface of the forearm, each consisting of 1000 units contained in 0.05 cc. of saline. Within 15 minutes 1 showed moderate erythema and whealing at the sites of injection which persisted for 30 minutes. There was flaring of some but not all of the old sites on the same arm, and this subsided within 2 hours. The other showed a marked erythema in 15 minutes with slight wheals at the sites of the intradermal injections, and in contrast developed, by the 18th hour, marked reddening and swelling at the sites of all injections with some induration which persisted for at least 96 hours after injection. In both individuals the original erythema and the whealing reactions subsided within 2 hours.

Because of the reactions shown, a series of patch tests was made to determine whether the eczematous type of hypersensitivity could be demonstrated. Similar patch tests were made also on 5 of the persons who had shown a tuberculin type of hypersensitivity to crystalline penicillin sodium on initial injection. The tests were made with commercial penicillin sodium, crystalline penicillin sodium, and corn steep liquor, using both normal skin areas and areas which had exhibited previously a tuberculin type of reaction following intradermal injection of penicillin sodium. Although all patch tests were negative, intradermal tests made at the same time with crystalline penicillin sodium again yielded a positive tuberculin type of reaction. From these results it is obvious that none of these test subjects exhibit the eczematous type of sensitivity to either crystalline or commercial penicillin. In this respect these people differ in their hypersensitive state from the individual previously described[7] who showed a tuberculin type of sensitivity to crystalline penicillin sodium and also gave a positive patch test at the site of a previous intradermal injection of either commercial or crystalline material. In order to make sure that the negative reactions were not the result of failure of the material to penetrate the horny layer and thereby reach the shock tissue, areas of the skin of 5 people who had shown a positive reaction following intradermal injection were sand-papered sufficiently to cause an occasional faint pin-point punctum of blood. Patch tests were then made on these sites. These tests were also negative, indicating that the negative patch tests resulted from the lack of a hypersensitive shock tissue rather than from inability of penicillin to penetrate the horny layer.

As stated previously, it was not possible to demonstrate passive transference of the sensitivity exhibited by persons who show a tuberculin type reaction on first contact with penicillin. An attempt was made, therefore, to transfer passively the hypersensitivity exhibited by individuals in whom the hypersensitive state had been induced by

intradermal injection. Four test subjects who had exhibited varying degrees of sensitivity were used and the P–K technique was followed. Passive transfer was attempted to 6 normal persons. Passive transfer antibodies (P–K reagins) could not be demonstrated. Precipitin tests made on the serum of the 4 test subjects were also negative.

One individual who had been a recipient for the passive transfer experiments, although showing no reaction directly after the attempted transfer, exhibited, beginning about 7 days later, a tuberculin type of reaction. This individual reported that on the 6th day following injection the injected areas had itched considerably. On examination on the 7th day his right arm presented 3 erythematous infiltrated areas corresponding to the sites where the penicillin had been injected 7 days previously. The sites where penicillin plus serum had been injected were slightly more inflamed and elevated than the site where the penicillin alone had been injected. The left arm which had received control injections of serum, saline and ragweed showed no reaction whatsoever. This person apparently developed a sensitivity of the tuberculin type as a result of 3 simultaneous intradermal injections of crystalline penicillin sodium of 1000 units each.

To determine whether the sensitivity to penicillin would also extend to the spores of *Penicillium notatum*, a heat-killed suspension was made containing 500,000 spores per cc. Intradermal injections of 0.1 cc. were given to 5 persons who exhibited a tuberculin type of hypersensitivity to penicillin. There were no immediate or delayed reactions. This is in accord with the studies of Feinberg[2] who noted that people sensitive to *Penicillium* sp. did not react to penicillin. We also tested the same 5 persons and several normal controls with various fungous extracts, namely, Trichophyton, Oidiomycin, Haplosporangin, Histoplasmin, Coccidioidin and Blastomycin. There were no significant differences between the penicillin-positive people and the normal controls in their reactions to these extracts.

Discussion. It would appear from the results of this investigation that a small, but substantial, percentage of the population is sensitive to crystalline penicillin sodium despite the fact that these individuals have had no contact with this material previously. Since the material at the test strength is not a primary irritant, a positive reaction indicates that these individuals are specifically hypersensitive to this material, and unless a radically new mechanism for such reactions is hypothesized, it must be assumed that these individuals have had previous contact with penicillin sodium or with an immunologically equivalent material. Contact with penicillin sodium as such can be arbitrarily eliminated. However, contact with *Penicillium* sp. appears to be quite likely since it is a fairly common genus of fungi. It may be postulated that this organism is not infrequently ingested or inhaled, producing in susceptible individuals a subclinical infection with a consequent alteration in their immunologic responses.

It is of interest that in the series reported by Lyons[5] and by Keefer[4] an average of about 4% of the individuals treated with penicillin

sodium exhibited an urticarial type of reaction, while in our series about 5% exhibited a tuberculin type of hypersensitivity following intradermal injections of this material. Only 2 hypersensitive persons in our investigations had therapeutic-sized amounts of penicillin. One of these received on one occasion about 10,000 units intravenously and on another occasion about 50,000 units intramuscularly. On neither occasion was there a systemic reaction despite the fact that this individual gave a strongly positive tuberculin type reaction to crystalline penicillin sodium. The other individual exhibited, beginning about 6 to 8 hours after receiving 50,000 units intramuscularly, a diffuse miliary papulovesicular dysidrosiform eruption which persisted for several days. His reaction was apparently identical to that described by Graves *et al.*[3] as were also his immunologic responses to penicillin.

It will be noticed that there was a rather striking disparity in the incidence of reactions produced by the intradermal injection of penicillin depending on the time between successive administrations and the route of administration. Where the intervals between repetitions were 5 days, a relatively high percentage of reactions was obtained in contrast to practically no reactions when the intervals were only 48 hours apart. Furthermore, reactors were obtained only when the penicillin was given intradermally. While it is realized that this series is much too small to have these differences assume any statistical validity and that other variables (such as sex and race) also differed in the series, the impression is gained that frequent injections of penicillin subcutaneously, intravenously, or intramuscularly are less likely to yield adverse reactions than similar injections made intradermally.

The reactions obtained following intradermal injection of penicillin sodium fall into two categories. In the case of the spontaneously sensitive individuals all reactions were of the tuberculin type. In this group there does not seem to be any eczematous or wheal (urticarial) component. In the individuals originally negative but who became hypersensitive following repeated intradermal injections of penicillin sodium the reactions, although eventually developing into a tuberculin type of hypersensitivity, may show transient reactions wheal-like in nature before this stage is reached. These transient reactions appear to be predicated on capillary damage or injury, and simulate in some respects the type of reaction seen in the Arthus phenomenon. The latter reaction, of course, is ordinarily brought about by repeated subcutaneous injections of a soluble protein, while in the case of penicillin sodium the injections were intradermal and the material nonprotein. Furthermore, when subcutaneous injections of penicillin sodium were made no reactions were obtained. A possible explanation for the similarity of the reactions obtained with penicillin sodium and those seen in the Arthus phenomenon is that when penicillin is injected subcutaneously or intramuscularly it is excreted very rapidly from the system. Furthermore, from other studies in this laboratory, it is obvious that the penicillin molecule has a strong avidity for protein since it readily conjugates with such substances. It is well known that

substances injected intradermally are excreted much more slowly than when injected by other routes of administration, and consequently it may be possible that penicillin sodium injected intradermally remains *in situ* for a sufficient period of time to combine with body proteins, thus forming a heterologous antigen in which the penicillin molecule acts as a hapten. When penicillin sodium is injected subcutaneously, rapid excretion does not permit sufficient time for the formation of such an antigen. It is possible also that penicillin sodium *per se* can act as an antigen. In this event the reason for the reactions obtained when it is given intradermally and lack of reaction when given subcutaneously may again be because of the time element. The fact that we failed to demonstrate precipitins in the individuals showing the reactions described, militates against the explanation that such reactions were of the nature of the Arthus phenomenon. Failure to demonstrate precipitins, however, may be explained on the basis that the antigen dilution method was used to determine the precipitin titer and this technique, as has been pointed out by Cannon and Marshall,[1] is not suitable for use with sera having low precipitin titers.* It may be that the reactions observed can be considered as the first stages of an Arthus phenomenon and that continued injection might have developed the more serious necrotic phenomenon and simultaneous development of high precipitin titers. Continued injection in the volunteer laboratory personnel, however, did not appear to be justified.

Summary and Conclusions. 1. Five % of 144 individuals tested with crystalline penicillin sodium exhibited a positive reaction of the tuberculin type, despite the fact that none of these individuals had had any prior contact with penicillin.

2. Repeated multiple intradermal injections of penicillin sodium cause the development in some people of reactions of the Arthus type, and some of these also developed a tuberculin type of hypersensitivity.

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* If, as suggested above, penicillin acts as a hapten, visible precipitation would not be expected to occur. However, precipitin tests on some of the test subjects repeated approximately 1½ months later with a conjugate of human plasma and crystalline penicillin were negative.

EFFECT OF SODIUM SALICYLATE ON THE SEDIMENTATION RATE OF ERYTHROCYTES IN VITRO*

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Interest in the salicylates has been renewed by Coburn's[2] work on the treatment of rheumatic fever with high doses of salicylates employing blood salicylate levels and determinations of the sedimentation rate as guides for therapy. Many clinicians use the sedimentation rate to judge the effectiveness of therapy in patients receiving salicylates. It is of interest therefore to examine the effect of salicylates on the sedimentation rate of erythrocytes *in vitro*.

In 1932, Bendien, Neuberg and Snapper[1] reported marked slowing of the sedimentation rate following the addition *in vitro* to the blood of at least 100 mg. per 100 cc. of sodium salicylate. In 1941, Lichty and Hooker[6] confirmed these findings and stated that the lowest concentration of salicylate necessary to cause slowing of the sedimentation rate was 90 to 120 mg. per 100 cc. which was at least 3 times the value given by Hanzlik[5] as an average blood level obtainable in rheumatic patients. Bendien, Neuberg and Snapper[1] attributed the action of the salicylates to an increased stability of the colloidal state of the plasma proteins. The plasma fibrinogen concentration, plasma viscosity and the red blood corpuscles were unaltered. This view is supported by the more recent experiments of Coburn,[3] showing that the addition of sodium salicylate to rabbit serum modifies the precipitation of serum proteins by sodium tungstate and also partially inhibits the precipitation of horse serum euglobulins by rabbit antiserum.

In the present experiments the *in vitro* effects of salicylates in concentrations comparable to therapeutic levels were investigated.

Methods. The following methods were used in all experiments unless modifications are noted specifically.

1. The *corrected sedimentation rate* (C.S.R.) was determined by the method of Rourke and Ernstene,[8] using as anticoagulant a dry mixture of 4 mg. of potassium oxalate and 6 mg. of ammonium oxalate for each 5 ml. of blood.

For the study of the effects of salicylate, the plasma was separated from the cells by slow spinning and transferred into test tubes in amounts of 2 ml. per tube; the sodium salicylate was then added in the form of a solution of 2 gm. in 100 ml. of isotonic sodium chloride solution. One tube was left without salicylate, as a control; to the others were added amounts to make concentrations of 12, 30, 60, 90, 120, 150, 180 and 210 mg. of sodium salicylate per 100 ml. of plasma. The quantities of diluent were kept the same in all tubes by the addition of physiologic saline solution in amounts inversely proportional to the quantities of sodium salicylate solution used. Plasma thus prepared was kept sterile and was left standing for various lengths of time. In order to determine the C.S.R. in such plasmas, fresh cells were obtained from

* This study was aided in part by a grant from the Ella Sachs Plotz Foundation, in recognition of Dr. Francis W. Peabody's services to the Foundation.

the same individual by slowly centrifuging oxalated blood and pipetting the cells into the prepared plasmas in amounts resulting in the original hematocrit value. Plasma and cells were left in contact for 30 to 120 minutes and the C.S.R. was then determined as usual. All results are given in millimeters per minute and are corrected for a hematocrit of 45%, according to the chart of Rourke and Ernstene.[3] The use of this chart in the presence of salicylate is justified because this salt does not alter the mean corpuscular volume and because the relation between C.S.R. and hematocrit was found to be unchanged by the addition of salicylate.

2. Different *plasma fibrinogen* levels were obtained in normal plasma by the addition of human plasma fibrinogen purified by electrophoresis.* The plasma fibrinogen determinations were done by the Cullen-Van Slyke method in citrated plasma.[4]

3. *Salicylate levels* in plasma and serum were measured by the method used by Coburn.[2]

4. The Beckman pH meter equipped with glass electrode served for the determination of the H ion concentration in the plasma.

Experiments. 1. The Effect of Sodium Salicylate on the C.S.R. of Normal Blood Adjusted to Different Plasma Fibrinogen Levels. By addition of human plasma fibrinogen to normal plasma, fibrinogen levels of 662, 467, 318 and 242 mg. per ml. were obtained. Each fraction of plasma was divided into 8 sub-fractions to which varying amounts of sodium salicylate were added. The plasma samples thus obtained contained 0, 30, 60, 90, 120, 150, 180 and 210 mg. of sodium salicylate per 100 cc. of plasma. One-half of each sample was left standing for 30 minutes. Fresh cells were then added and the C.S.R. determined after another 30 minutes. To the remaining half of each sample fresh cells were added after plasma and salicylate had been left in contact for 24 hours at room temperature and the C.S.R. was determined 30 minutes later. A few samples were treated in the same manner except that the plasma and salicylate were left in contact for 24 hours in a water bath at 37° C. *Results:* (Chart 1, left side, and Chart 2.) In the plasma which had stood for 30 minutes in contact with salicylate marked slowing of the C.S.R. was observed at drug levels of 90 mg. per 100 ml. or higher. When the contact of plasma and salicylate extended over 24 hours at room temperature this effect was more marked and occurred at levels as low as 30 mg. per 100 ml. The C.S.R. was not significantly altered in the salicylate-free controls. When plasma was incubated for 24 hours at 37° C. even the controls were significantly slowed and consequently the C.S.R. in samples containing salicylate was no longer readable.

2. Effect of Sodium Salicylate on the C.S.R. of Blood From Patients With Various Diseases. (Chart 1, right side.) Blood with accelerated C.S.R. was taken from patients with various diseases, and the plasma left in contact with sodium salicylate for 24 hours at room temperature. Fresh cells of the same individuals were then added and the C.S.R. determined. *Results:* A marked reduction of the C.S.R. followed the addition of sodium salicylate in all these cases and amounts comparable to therapeutic levels reduced the C.S.R. to normal values.

* The fibrinogen used was a sample prepared by the Harvard Plasma Fractionation Laboratory and obtained through the courtesy of Prof. E. J. Cohn.

3. Possible Mechanisms of Effect. (*a*) Numerous *plasma fibrinogen* concentrations were determined in plasmas containing varying amounts of sodium salicylate. Even in samples showing extreme retardation of the C.S.R. the plasma fibrinogen levels were not significantly altered.

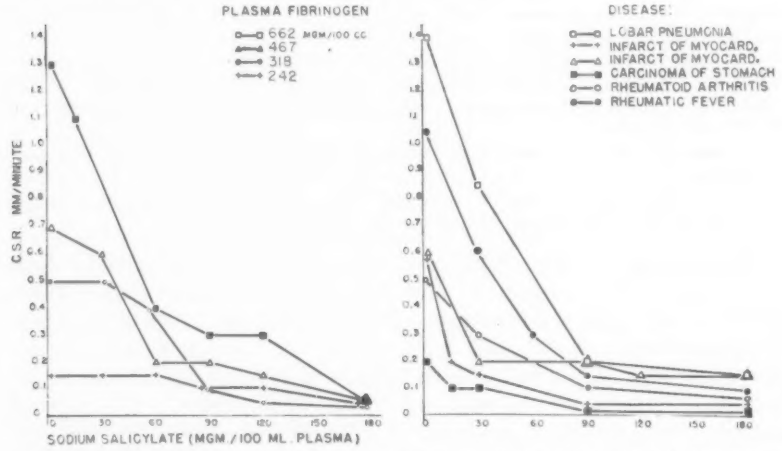

Chart 1.—Slowing of sedimentation rate by sodium salicylate *in vitro* in blood from various patients (right) and in normal blood adjusted to different fibrinogen levels by addition of purified fibrinogen (left).

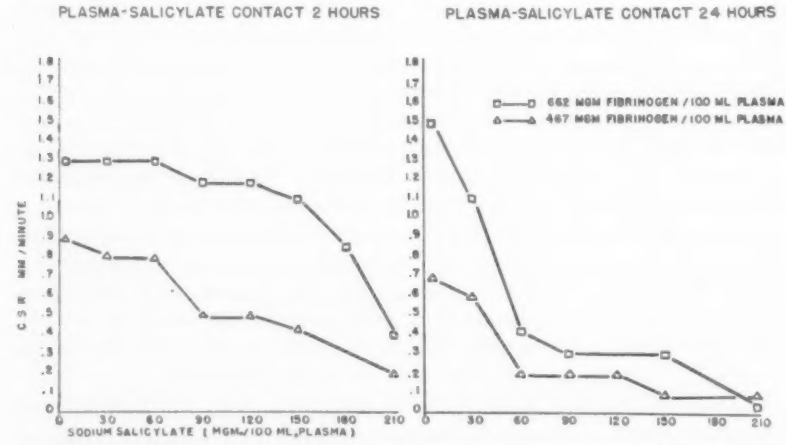
PLASMA-SALICYLATE CONTACT 2 HOURS
PLASMA-SALICYLATE CONTACT 24 HOURS
662 MGM FIBRINOGEN / 100 ML PLASMA
467 MGM FIBRINOGEN / 100 ML PLASMA
C S R MM / MINUTE
SODIUM SALICYLATE (MGM./100 ML. PLASMA)

Chart 2.—Slowing of sedimentation rate by sodium salicylate *in vitro* in blood adjusted to different fibrinogen levels.

(*b*) *Red blood corpuscles* were suspended in normal plasma after having been exposed to mixtures of plasma and salicylate which had been standing at room temperature for 24 hours. In all cases, even after remaining in contact with such mixtures for 2 hours, the C.S.R. of these erythrocytes in normal plasma was the same as before exposure to salicylates.

(*c*) The *effect of other sodium salts* (Chart 3) was tested by replacing the sodium salicylate by equal amounts of sodium benzoate and sodium bicarbonate. Neither of those salts had any effect nor did sodium bicarbonate inhibit the action of the sodium salicylate.

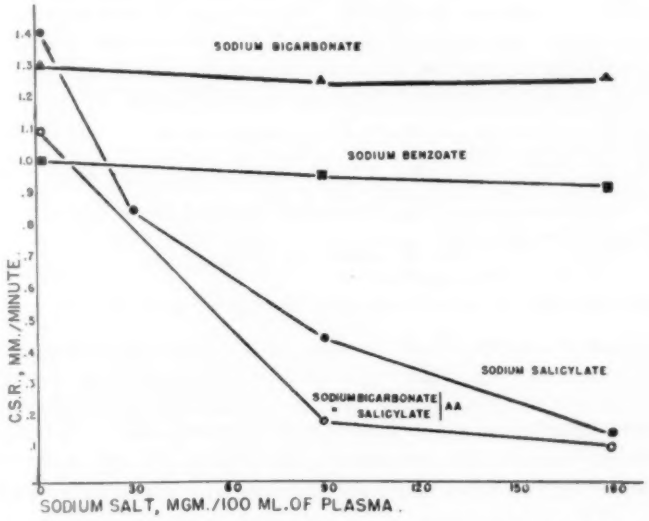

CHART 3.—Effects of sodium salts upon sedimentation rate *in vitro*.

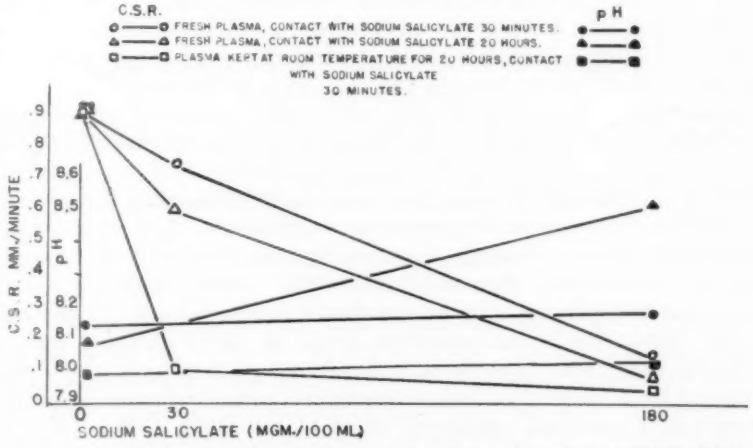
C.S.R.
FRESH PLASMA, CONTACT WITH SODIUM SALICYLATE 30 MINUTES.
FRESH PLASMA, CONTACT WITH SODIUM SALICYLATE 20 HOURS.
PLASMA KEPT AT ROOM TEMPERATURE FOR 20 HOURS, CONTACT WITH SODIUM SALICYLATE 30 MINUTES.
pH
C.S.R. MM./MINUTE
SODIUM SALICYLATE (MGM./100 ML.)

CHART 4.—H^+ ion concentration in plasma in relation to sodium salicylate effect.

(*d*) If the *salicylate radical* became *conjugated with fibrinogen* (Table 1) it would be likely that part of the salicyl radical would no longer be contained in the serum after coagulation of the fibrinogen by recalcification and that the plasma might lose free salicyl radical through prolonged contact with it as the method used for its determination is specific for *free* salicyl. The experiment tabulated in Table 1 demon-

strates that this does not take place. Some salicyl radical is lost to the erythrocytes after 24 hours as described earlier by Bendien, Neuberg and Snapper.[1]

TABLE 1.—THE FATE OF SODIUM SALICYLATE IN FULL BLOOD, PLASMA AND SERUM AFTER STANDING AT ROOM TEMPERATURE FOR 24 HOURS

No.	Description of sample examined	Salicylate (mg. per 100 ml.) After 2 hrs.	After 24 hrs.
1	Salicylate solution and saline (5 ml. of each)	114	117
2	5 ml. of salicylate solution, 4.5 ml. saline, 0.5 ml. of 2.5% sodium citrate	110	112
3	5 ml. of salicylate solution, 4.5 ml. of serum ,0.5 ml. of 2.5% sodium citrate	97	93
4	5 ml. of salicylate solution, 4.5 ml. of plasma, 0.5 ml. of 2.5% sodium citrate	96	109
5	Same as No. 4 after recalcification and centrifuging off the fibrin clot	96	108
6	Same as No. 4 with cells added, left in contact for 24 hours, then centrifuged off	..	70

NOTE.—The technical error of the method in our hands is approximately + or − 15%.

(*e*) *Changes in the pH of the plasma* (Chart 4) during standing at room temperature and after addition of sodium salicylate were investigated. According to Nichols[7] there is a difference of opinion as to whether variations in pH influence sedimentation rate. In the present experiments there were measurable changes in H^+ ion concentration but there was no causal relationship between these changes and those of the C.S.R.

(*f*) *Standing at room temperature* may be an important factor. Not only is the salicylate action increased, but mere standing of the plasma alone for 20 hours at room temperature considerably increases the effect of sodium salicylate when this is added thereafter and the C.S.R. determined within 30 minutes after addition of the salt.

Discussion. Thus, sodium salicylate, *in vitro*, has the effect of slowing the sedimentation rate by a mechanism as yet unexplained, but probably related to changes in the stability of the colloidal state of the plasma.[1,3] This effect takes place immediately following the addition of sodium salicylate in concentrations considerably larger than those reached *in vivo*, as previously shown by Bendien, Neuberg and Snapper[1] and by Lichty and Hooker.[6] When the contact between sodium salicylate and plasma is prolonged for 20 hours at room temperature under sterile conditions, salicylate levels as small as those seen in patients under salicylate therapy cause marked slowing of the C.S.R. Leaving pure plasma at room temperature, before salicylate is added, results in a markedly enhanced effect of the latter. This effect of salicylate is non-specific and occurs in blood artificially enriched in fibrinogen as well as in blood of patients with various diseases.

Conclusion. It seems possible that this property of sodium salicylate, demonstrable *in vitro*, may partly account for the remarkable slowing of the sedimentation rate seen in some patients who receive salicylates. This problem deserves further investigation.

Summary. 1. Sodium salicylate *in vitro* causes a marked reduction of the sedimentation rate of erythrocytes, particularly if it is accelerated.

2. In fresh plasma this effect takes place at salicylate levels of about 90 mg. per 100 ml.

In plasma which has been kept at room temperature for 24 hours the effect takes place at levels of 25 to 30 mg. of salicylate per 100 ml. of plasma.

When salicylate is left in contact with fresh plasma for the same length of time, the slowing of the sedimentation rate occurs at low levels. The standing of plasma at room temperature has an insignificant effect on the sedimentation rate of fresh red blood corpuscles in such plasma.

No demonstrable changes of plasma fibrinogen or red cells are caused by sodium salicylate and changes of the pH in the plasma do not account for the effect of sodium salicylate on the sedimentation rate. The effect is inherent in the salicylate radical, as sodium benzoate and sodium bicarbonate are ineffective.

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THE ERYTHROCYTE SEDIMENTATION RATE IN RHEUMATIC FEVER

Its Significance in Adolescent and Overweight Children

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An important problem which arises in the management of rheumatic fever is that of the length of the period of bed rest following the acute stage. Too short a period of bed rest may cause additional damage to the heart, whereas an unnecessarily long period is undesirable for economic and psychologic reasons. In the absence of a specific test for the state of activity of the rheumatic process, non-specific ones are employed. The criteria in use include normal temperature and pulse rate, white and red blood corpuscle counts and erythrocyte sedimentation rate (ESR). All of these serve also as criteria of absence of infection or inflammation of any kind in the body.

Of these tests, the sedimentation rate is in the great majority of cases the most sensitive. After physical findings have become stabilized, the symptoms of active rheumatic infection have disappeared,

and the temperature, pulse rate, respiratory rate and blood counts have returned to normal limits, the rate of erythrocyte sedimentation often remains higher than the accepted normal values, and higher than is normal for the patient. Accordingly, the ESR has become accepted as the finest criterion of complete clinical quiescence of the rheumatic process, and convalescents from rheumatic carditis are maintained in complete bed rest until the sedimentation rate finally reaches the accepted normal limits.

The application of the erythrocyte sedimentation test in this way depends upon the assumption that there is at the time no other process in the body which of itself increases the sedimentation rate. As the test is generally understood, this means that one assumes there exists no other major area of inflammation, in its broad sense of infection, tissue destruction or tissue absorption. This assumption is usually taken to be satisfied if the rheumatic patient shows no evidence of acute infection at the time of the test and has had no acute infection within 2 or 3 weeks. In a patient otherwise apparently well, the failure of the result of the sedimentation test to return to accepted normal values is regarded as evidence of continuing activity of the rheumatic process.

In the course of the past few years the author has, however, observed a few children convalescing from acute rheumatic carditis in whom the ESR did not return to normal limits for very considerable periods of time after all other indications of rheumatic activity had passed. These children were almost all girls, in the adolescent or pre-adolescent age group. About half of these patients were overweight. Finally, when the suspicion became strong that in these particular children the erythrocyte sedimentation test was not a measure of the degree of rheumatic activity, they were gradually allowed increasing physical activity up to the limit of normal activity of the quiescent rheumatic patient.

Since it was, in effect, being assumed that the rheumatic process was quiescent, despite the elevated ESR, it was particularly important to determine whether this treatment was justified by the subsequent clinical course, after the resumption of physical activity. Accordingly, careful clinical observations were continued during this period.

Clinical Material. The 9 children whose histories will be summarized were under the author's care at the Children's Seashore House for Invalid Children at Atlantic City. Two of them were later followed in Philadelphia at the Cardiac Clinic of the Children's Hospital. They were admitted to the Children's Seashore House from hospitals in Pennsylvania and New Jersey in various stages of convalescence from rheumatic carditis. The ages ranged from 9 to 16 years. They were all girls with the exception of 1 boy who was rather obese. Several of these girls were also overweight. During the 3½ year period during which observations were made, other rheumatic children convalescing from carditis were observed and treated by the author in the same institution in exactly the same way as these 9 patients. The entire group included 400 patients. They were distributed among the ages of 5 to 16 years and rather evenly between the sexes. In all of these children, the return of the ESR toward normal limits could be observed, or, in some quiescent cases, its value was within accepted normal limits when they entered the Children's Seashore House.

Methods. During the entire period of observation of each child, both before and after the patient was allowed out of bed, the following examinations were made periodically:

1. Examination of the heart, including the determination of the position of the apex beat, quality of sounds, murmurs and their transmission, thrills and friction rubs, and cardiac rate and rhythm.
2. General physical examination, including a check on signs of circulatory failure, chorea, pharyngitis, rash, subcutaneous nodules and weight loss.
3. Questioning of patients and nurses as to appearance of characteristic symptoms associated with rheumatic activity such as headache, anorexia, nausea, vomiting, pain (in precordium, chest, abdomen or joints), epistaxis, and general lack of well-being.
4. Recording of such episodes as pharyngitis or other respiratory infections.
5. Laboratory examination, including determination of hemoglobin concentration in blood, red and white corpuscle counts and erythrocyte sedimentation rate. These determinations were always made at the same time of day. Bacteriologic cultures of the nasopharynx and throat were also made at regular intervals. The ESR was measured in mm. of free fall per hour, as described below.

Results. The period of treatment by bed rest, and the ESR at the end of that time, are shown in Table 1. In 7 of the 9 cases, the patients were kept on bed rest for over 1 year before it was decided to allow them up in spite of an unduly high ESR. In 1 extreme case 2 years elapsed. The ESR at the time these patients were allowed their first activity out of bed ranged from 20 to 36 mm. of free fall per hour. The children were observed for periods averaging 7.3 months, thereafter. In 1 case the ESR fell substantially during this time, and in 2 other cases there was a slight fall in the ESR (of 6 or 7 mm. per hour) after the patient was allowed to resume activity.

TABLE 1.—CASES OF PROLONGED ELEVATION OF THE ESR

Case No.	Age	Sex	Months of bed rest at CSH before allowed up	Cardiac status at that time		ESR at that time (mm. of free fall per hr.)	Corresponding ESR at 45% packed RBC volume*	Length of observation thereafter (mos.)	ESR at time patient last seen
				Position of apex beat (cm. from mid-line)	Cardiac lesion				
40	13	F	18	7.6	None	20	22	3	20
117	12	F	18	7.2	None	26	28	15	14
124	10	F	24	7.0	M.I.	32	32	5	30
136	9	F	16	7.0	None	30	25	20	28
157	16	F	15	11.2	M.I., A.I.†	36	30	3	32
158	15	F	17	10.6	M.I.	32	26	6	30
216	10	F	12	6.8	None	26	22	5	28
222	14	M	11	8.2	M.I.	24	21	5	18
381	13	F	5	9.0	M.I.	30	26	4	23

* Using the Ordway-Singer nomogram[13] derived from the Rourke-Ernstene chart.[15]
† Mitral insufficiency, aortic insufficiency.

Table 1 shows also that the degree of cardiac damage varies quite widely among the patients described. Of the 5 apical systolic mur-

murs corresponding to the notation of mitral insufficiency, 1 was transmitted to the posterior axillary line, 2 to the mid-axillary line, and 2 were localized to the apex. Some of the results of the periodic examinations of the children are shown in the chart for each patient, for the entire period of observation.

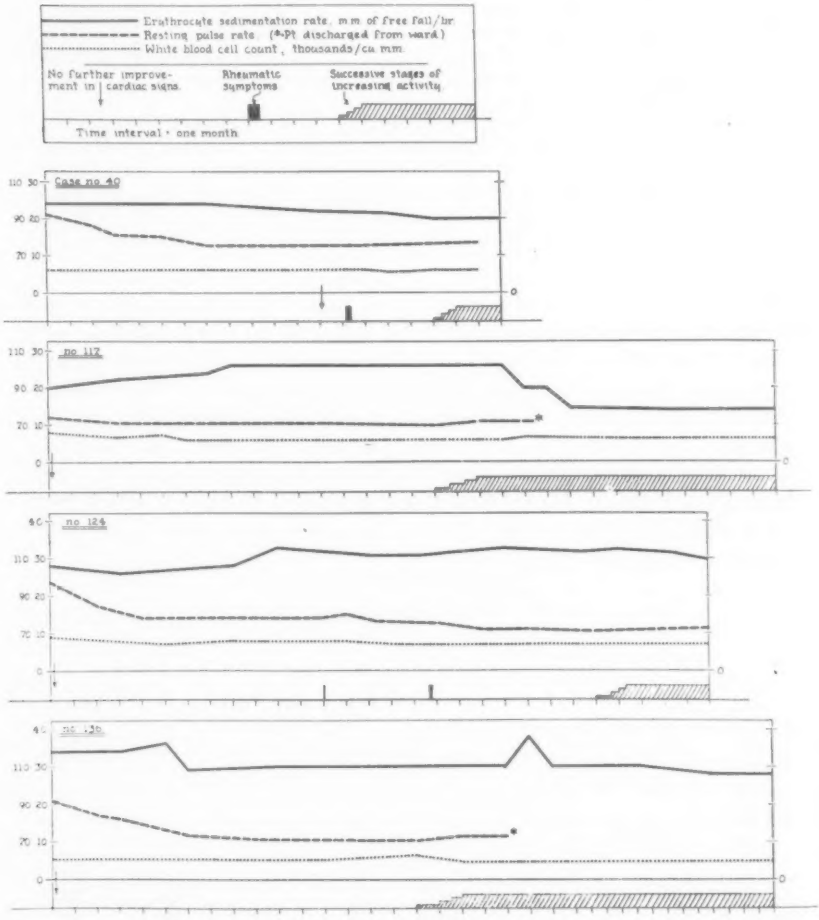
Erythrocyte sedimentation rate, mm. of free fall/hr.
Resting pulse rate (*-Pt discharged from ward.)
White blood cell count, thousands/cu. mm.
No further improvement in cardiac signs.
Rheumatic symptoms
Successive stages of increasing activity
Time interval - one month
Case no. 40
no. 117
no. 124
no. 130

CHART 1.—Effect of increasing activity on ESR, resting pulse rate, and white blood cell count in 4 cases.

1. Examination of the heart: In general, successive examinations showed a tendency of the findings to change in the direction of normal values, until they became constant. The vertical arrow in the charts indicates the time at which the cardiac findings became constant. In some cases, there was no improvement after the admission examination.

2. Symptoms and general physical signs characteristic of rheumatic infections: These, unless clearly attributable to a cause other than the

rheumatic infection, are represented by a vertical line on the base line corresponding in breadth to the duration of the symptoms.

3. Resting pulse rate: These were averaged for each month from weekly rates determined during sleep.

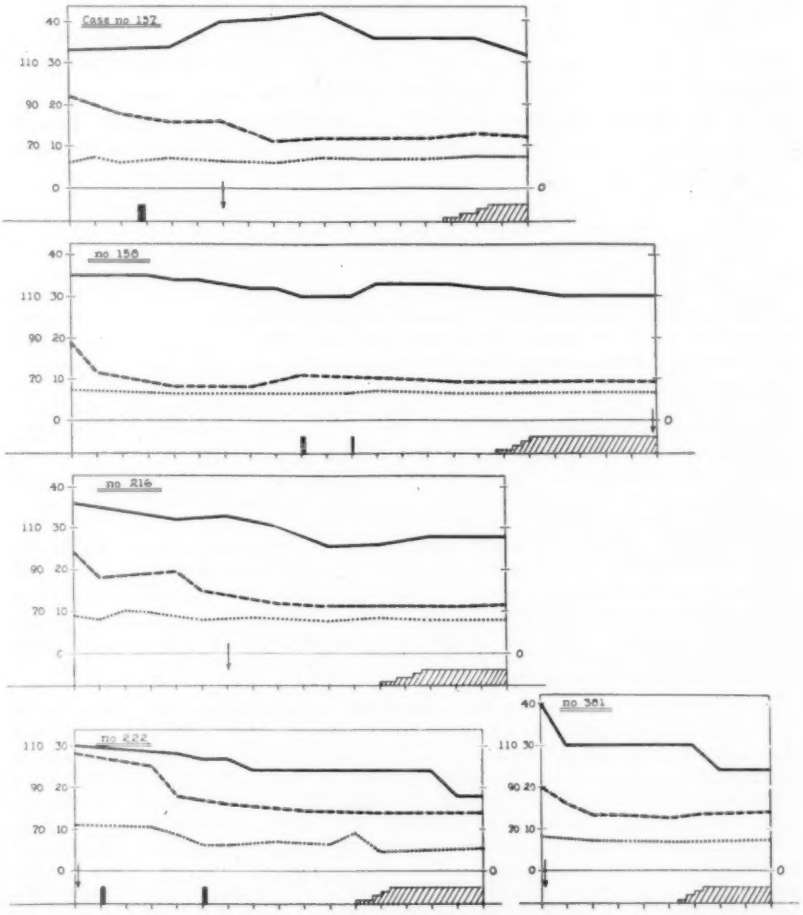

CHART. 2.—Effect of increasing activity on ESR, resting pulse rate, and white blood cell count in 5 cases.

4. Increasing amounts of activity permitted the patient are indicated by the stepwise rise of the line in the lower right corner of each chart: bathroom privileges, then 1, 2 and, finally, 4 hours out of bed. The first 2 hours out of bed were given over to the supervised activity of the classroom and the occupational therapy shop. Markers along the base line indicate months.

It is the purpose of the chart to indicate significant developments in the clinical course of each patient under discussion. In addition to

the signs, symptoms and tests indicated, there was no weight loss, fever, increase in respiratory rate or decrease in hemoglobin value during the period of observation following resumption of physical activity. As will be seen in the charts, in none of these children was there any indication, by any of the tests mentioned, that the patients had been allowed out of bed prematurely.

Control observations were made on 391 other children who completed their convalescence from rheumatic fever at the Children's Seashore House. With the few exceptions indicated below, the ESR fell in the usually observed manner to 15 mm. per hour or below, usually within about 1 month of the cessation of other conventional indications of rheumatic activity. The fall of the ESR from values of over 40 mm. of free fall per hour usually required only a few weeks.

The Technique Employed by the ESR Test. The erythrocyte sedimentation rate was determined in mm. of free fall per hour by recording the height of the erythrocyte column at 5 minute intervals for ½ hour. The time-lag due to the rouleaux formation was eliminated by beginning the readings only after some observable sedimentation had taken place. The error due to packing of red blood corpuscles was obviated by using a 100 mm. tube and by dropping the last reading or two if they fell out of the arithmetic progression. In this way the determination of rate of free fall of rouleaux is based on a number of mutually corroborative observations during successive intervals rather than one or two. The measurement of this physical property of the blood is the basis of all techniques of determining the ESR now in general use.[7,12,15,19,23]

No attempt can be made here to enter into the vexed question of the necessity for and the correct method of routine "correction for anemia."[1,2,4–6,8–11,15–18,20–22] This question is not of decisive importance for the purposes of this paper, since the hemoglobin values and packed red corpuscle volume percentages of the patients described were in no case far from normal. This was probably a consequence of months of good institutional care in the absence of active rheumatic disease. As Table 1 shows, in no case was the difference between the original and adapted ESR greater than 6, and in 2 cases the adjustment to 45% packed red corpuscle volume gave a higher result.

The question of normal limits of the ESR is, again, not within the scope of this paper. During the past 4 years the ESR was determined in this way for 400 patients who convalesced in this institution from rheumatic carditis, and 82 patients with chorea. In addition to the rheumatic group there were patients convalescing from nephritis, upper respiratory infection, malnutrition, and so forth. Almost all of these children reached an ESR of below 15 mm. per hour of free fall or showed such an ESR on admission. The lowest recorded was 3 mm. per hour. The only exceptions to this range in the absence of intercurrent infection were 3 rheumatic patients, 2 of whom were severely anemic because of symptomatic epistaxis, and 5 other rheumatic patients, all girls, who reached levels of between 15 and 18 mm. per hour. These last were not included in this paper because their ESR was so near the normal range for the group.

The values of the ESR shown in Table 1 are, then, definitely out of the range of normal for the group. They would all be considered abnormal according to the authors of four of the five techniques mentioned above, and 6 of the 9 would be considered outside normal limits by the fifth method, the Rourke-Ernstene technique.[15]

Discussion. The data presented in this paper have both theoretical and practical implications. The theoretical implications are quite obscure, inasmuch as we understand today neither the basis for increased ESR nor the mechanism of rheumatic infection. The ques-

tion arises: Are these instances of persistent elevation in ESR a result of interrelation of the rheumatic process and a factor present in some adolescent children, or are they merely a result of random sampling in a group of adolescents, in which some instances of elevated ESR are found? The latter alternative, in turn, poses a prior question: Is there, in the distribution of ESR values in adolescents, a number of apparently normal healthy children, especially girls, whose ESR falls outside the general range of normal values?

In the standardization of the various techniques of determining the ESR there has been no emphasis on normal values in the age-sex group under consideration. Two studies have been reported, however, on the range of ESR observed in presumably normal girls in the adolescent and pre-adolescent age group. In one study[14] it was found that although the mean ESR of 87 adolescent subjects was 10 mm. per hour, 5% showed values over 40. In another study,[3] 327 normal girls of adolescent and pre-adolescent age were examined by the Cutler technique. It was found that 8% of the subjects had ESR values ranging from 14 to 25, the others falling within the normal limits found by Cutler in standardizing his method. The question of latent infection as a possible cause of the higher values found in this group was subjected to very careful control, but months of observation thereafter revealed no pathologic cause for the higher values. A greater mass of data would seem to be necessary if this is to be accepted as a part of the natural history of adolescence. If such confirmation is made then, as further data are accumulated on the distribution of values of ESR in healthy and in rheumatic adolescent girls, it may become possible to show whether the elevated ESR values found in the rheumatic groups are simply a result of random sampling of an effect of adolescence, or whether they result from an interaction of phenomena. It should also be of considerable interest to determine the distribution of ESR values in adolescent girls convalescing from other chronic diseases which elevate the ESR, such as tuberculosis and nephritis.

The observations reported here would also seem to have a practical implication for the management of convalescence from acute rheumatic carditis in the case of adolescent patients.

It is unfortunate that in rheumatic fever the more specific parts of the clinical picture, cardiac signs and symptoms, usually return toward normal limits earlier in convalescence than do the non-specific signs. The erythrocyte sedimentation test bears the special responsibility of being used in the great majority of cases as the criterion for beginning the increase in the patient's activity. The observations presented above would seem to affect the interpretation of an elevated ESR in rheumatic fever in adolescent patients, especially girls, when it persists for some time as the only indication of activity of the rheumatic process.

An examination of the clinical chart will show that in such cases a number of months may be spent by the patient in bed while the ESR remains elevated as the only indication of rheumatic activity, and this prolonged stay in bed is not well borne by children who are not actually ill. This is especially true in the older age groups among children, in

which the phenomenon has been observed. Under these circumstances it is, after a time determined by clinical observation, both unnecessary and harmful to continue complete bed rest while waiting for the ESR to return to normal limits.

It need hardly be said that where any doubt exists as to the status of the patient, complete bed rest is advisable and should be continued. Certainly it is far better to err in the direction of too long a period of complete bed rest than to allow the patient increased activity prematurely. Finally, the continued examinations which would invariably be made under the circumstances, as the patient is carefully permitted increasing activity, would serve to confirm the clinical judgment in such cases.

No attempt has been made to estimate the expected frequency of the phenomenon described here because of the small number of cases observed and because of the lack of general agreement as to the normal range of ESR values. For orientation, however, it may be indicated that within this group of 400 convalescent rheumatics, the 9 cases described here represent 2.3% of the total, or 3.6% of the 248 patients who fell in the age range of 9 to 16 years. In the girls' wards the 8 cases represent 3.7% of the 215 patients, or 6% of the 133 girls in the 9 to 16 year range.

The term "rheumatic activity" has been avoided as much as possible because of our present lack of understanding of the nature of the rheumatic process and the consequent subjective factor involved in the use of the term. The children described in this paper have not been identified as "active" or "inactive rheumatics" in the terminology of rheumatic disease. Rather the quiescence of the rheumatic process affecting these children at the time they were allowed up has been indicated in terms of their subsequent tolerance of progressively increasing exercise, as observed data in the clinical charts. This is, in fact, the practical criterion in the management of convalescence from rheumatic carditis when one considers allowing the patient up.

It is of interest to report, in this connection, that of the control patients, 3 children who were allowed out of bed after the subsidence of all signs of rheumatic infection and the fall of the ESR to normal levels, in the usual manner, showed clinical evidence immediately thereafter that they had resumed activity prematurely. These children were returned to bed; their ESR values fell again, and the subsequent clinical course was uneventful.

In considering the possibility that the persistence of the elevated ESR in the patients described might be due to an unrecognized smouldering rheumatic lesion, it is pertinent to point out that the degree of cardiac damage was found to vary quite widely among the group, and that in 4 of the 9 no cardiac lesion was demonstrable during the greater part of their convalescence.

Summary. Four hundred children, 215 of whom were girls, were observed during their convalescence from episodes of rheumatic carditis. In 9 of these patients, 8 girls and 1 boy, ranging from 9 to 16 years of age, the ESR remained persistently elevated long after the other signs,

symptoms and tests for active rheumatic infection had returned to normal or become stationary. These patients were ultimately allowed out of bed while the ESR was still elevated. Continued clinical observation following the resumption of physical activity failed to reveal any indication that these children had been allowed out of bed prematurely.

Some theoretical and clinical implications of these data are discussed.

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EXPERIMENTS ON COMPONENTS A AND B (QUICK) OF PROTHROMBIN

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In 1943, Quick[1] observed that if stored human plasma and plasma from a dicumarolized dog, each having a low prothrombin level as measured by the Quick test, were combined in equal amounts, the resulting mixture showed a remarkable restoration of prothrombin activity. It was his hypothesis that prothrombin must be a complex of at least 2 factors, component A which disappears from stored blood or plasma and component B which becomes low during dicumarol administration. A clinical application of this discovery was at hand.

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If hemorrhage or other emergency made it imperative to restore the prothrombin level in a dicumarolized patient, stored blood or plasma should be as effective as the fresh.

It seemed desirable to repeat and amplify the experiments of Quick with several significant changes in the procedure which would make the experiments *in vitro* more comparable to the proposed clinical treatment. Quick's experiments involved a heterogeneity of species, *i. e.*, human stored plasma was mixed with the dog's dicumarolized plasma. After corroborating his findings (Group 1 experiments described below) we varied the experiment by mixing stored human plasma with dicumarolized human plasma (Group 2 experiments) and mixing the corresponding plasmas of the dog (Group 3 experiments). Furthermore, in his original tests Quick used plasma from blood in which sodium oxalate had been used as the anticoagulant. Since ordinary blood bank plasma contains an excess of sodium citrate to prevent clotting, it remained to be seen if it had the same restorative effect as oxalated plasma (Group 4 experiments).

In this investigation, the usual Quick prothrombin test was performed, using rabbit brain thromboplastin.[2] In a small test tube are placed 0.1 cc. of plasma and 0.1 cc. of thromboplastin solution. The tube is put in a water bath at 37° C. and 0.1 cc. of 0.025 M calcium chloride is added. The time from this addition to the formation of the clot is measured with a stop watch. From an empirically constructed curve, the prothrombin concentration in per cent of normal may be estimated from the prothrombin time.

Group 1 Experiments. This is the original experiment of Quick, involving the combination of human stored and dog dicumarolized plasmas. In Table 1, it may be seen that his results were duplicated.

TABLE 1.—MIXTURE OF STORED HUMAN PLASMA AND DICUMAROLIZED DOG PLASMA

	Prothrombin time in sec.	% of normal
Experiment 1:		
(*a*) Human plasma, stored 10 days	32	25
(*b*) Dog plasma, after feeding dicumarol	22	35
Equal parts of (*a*) and (*b*)	11	<100*
Experiment 2:		
(*a*) Human plasma, stored 37 days	120	>1
(*b*) Dog plasma, after feeding dicumarol	28	20
Equal parts of (*a*) and (*b*)	12	<100*

* Calculated on the basis of human plasma.

Group 2 Experiments. In these experiments, human dicumarolized plasma was substituted for the dog plasma of the preceding group. Experiments 3 and 4 reported in Table 2 are typical of 7 performed. In Experiment 5, fresh human plasma as well as stored plasma was used.

Group 3 Experiments. In these experiments, stored dog plasma was mixed with dicumarolized dog plasma. It was found that component A of prothrombin in the dog is much more stable than it is in man. When this plasma was stored, the prothrombin time remained approximately normal for 4 weeks, after which it became prolonged and was usually infinity at the end of 8 weeks. In Table 3, it is seen that

in Experiment 7, the combination of the 2 dog plasmas, each having an apparent prothrombin concentration of zero, resulted in a mixture with a prothrombin time of 12 seconds (60%).

TABLE 2.—MIXTURE OF HUMAN STORED AND DICUMAROLIZED PLASMAS

	Prothrombin time in sec.	% of normal
Experiment 3:		
(*a*) Human plasma stored 8 days	38	20
(*b*) Human dicumarolized plasma	32	15
Equal parts of (*a*) and (*b*)	20	65
Experiment 4:		
(*a*) Human plasma stored 27 days	40	5
(*b*) Human dicumarolized plasma	25	30
Equal parts of (*a*) and (*b*)	18	70
Experiment 5:		
(*a*) Fresh human plasma	13	100
(*b*) Human plasma stored 14 days	36	20
(*c*) Human dicumarolized plasma	45	5
Equal parts of (*a*) and (*c*)	16	70
Equal parts of (*b*) and (*c*)	16	70

TABLE 3.—MIXTURE OF STORED AND DICUMAROLIZED PLASMAS OF THE DOG

	Prothrombin time in sec.	% of normal
Experiment 6:		
(*a*) Dog plasma stored 51 days	∞	0
(*b*) Dicumarolized dog plasma	29	20
Equal parts of (*a*) and (*b*)	15	50
Experiment 7:		
(*a*) Dog plasma stored 64 days	∞	0
(*b*) Dicumarolized dog plasma	∞	0
Equal parts of (*a*) and (*b*)	12	60

TABLE 4.—EFFECT OF CITRATED PLASMA

	Prothrombin time in sec.	% of normal
Experiment 8:		
(*a*) Fresh human plasma, citrated	15	100
(*b*) Citrated human plasma, stored 3 mos.	∞	0
(*c*) Dicumarolized human plasma	25	30
Equal parts of (*a*) and (*c*)	18	65
Equal parts of (*b*) and (*c*)	18	65
Experiment 9:		
(*a*) Fresh human plasma, citrated	13	100
(*b*) Citrated human plasma, stored 3½ mos.	∞	0
(*c*) Dicumarolized human plasma	45	5
Equal parts of (*a*) and (*c*)	18	65
Equal parts of (*b*) and (*c*)	18	65

Group 4 Experiments. The anticoagulant used in the plasmas in the above experiments was sodium oxalate, 0.5 cc. of 0.1 M sodium oxalate being used for each 4.5 cc. of blood. Blood taken for the Henry Ford Hospital blood bank is kept fluid by adding 100 cc. of 2.5% sodium citrate to 500 cc. of blood. It seemed desirable to repeat the experiments using such citrated human blood. In a number of preliminary tests, it was found that when either of the above anticoagulants was used, identical prothrombin times were obtained from the resulting plasmas. The experiments detailed in Table 4 were then carried out. Citrated plasma, stored 3 months or longer was as efficacious as fresh plasma in the restoration of dicumarolized plasma.

Summary. 1. The experiments of Quick which suggested the hypothesis that prothrombin consists of at least 2 components have been corroborated and amplified.

2. The combination of equal volumes of stored human plasma and plasma from a dicumarolized person gives a mixture with a Quick prothrombin level of from 60 to 70% of normal. The same is true of the corresponding plasmas of the dog.

3. Fresh human plasma was not superior to stored plasma in such restoration of prothrombin.

4. The presence of sodium citrate in excess (as in blood bank plasma) did not affect this restorative property.

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HEMOLYTIC TRANSFUSION REACTIONS DUE TO THE Rh FACTOR

Report of 2 Cases

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The present conception of atypical agglutinins as a cause of transfusion reactions originates from the significant observations made by Levine and Stetson in 1939.[1] They described an antibody, responsible for a transfusion reaction, which agglutinated 80% of human Group O bloods and which was "independent of the M, N and P factors." Moreover, Levine and Stetson recognized the clinical significance of their findings and pointed out that beneficial transfusions could be obtained by the proper selection of donors whose cells failed to react with the atypical agglutinin; and that the immunization of the mother in their case was due to fetal tissues inherited from the father. These studies, together with the discovery of the Rh factor by Landsteiner and Wiener, and the detection of atypical antibodies in cases of repeated transfusions[4,11] have stimulated renewed interest in reactions following the infusion of blood. Patients with various blood dyscrasias are commonly given numerous transfusions over an extended period of time so that adequate opportunity for iso-immunization exists. Reactions are believed to occur more frequently in this group,[4] but careful investigation often fails to reveal an appropriate cause. The purpose of this report is to present 2 cases in which proof was obtained that the Rh factor was responsible for the transfusion reactions.

The first patient, H, was a 24 year old white male with far-advanced Hodgkin's disease, belonging to the blood Group O, Type Rh negative. From June 9 to June 27, 1944, while in another general hospital, he received 4 transfusions without reaction. On July 1 an infusion of

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washed red blood cells resulted in hives and dyspnea; this was followed by icterus, which, however, persisted and may have been due to hepatic metastases already known to exist. He was admitted to this hospital on July 5, 1944. During the following 15 days he was given 4 transfusions of citrated blood and 2 red cell infusions. With each of these he experienced reactions which consisted of chill, usually developing 1 to 2 hours after transfusion, and fever ranging from 101.4° to 104.4° (Table 1). On one occasion (July 20) hemoglobinuria followed a severe chill. All bloods given were "compatible" as judged by carefully performed cross-matchings using the test-tube technique recommended by Levine *et al.*[2] The data in Table 1 summarize the clinical and laboratory results on the donors used for transfusion.

TABLE 1.—TRANSFUSIONS, PATIENT H

Date 1944	Reaction	Donor	Agglutination of donors' cells by serum: Anti-Rh	Agglutination of donors' cells by serum: Patient H (7-29)
7- 7	Chill, temp. 104.4°	O	+	+
7- 8	Chill, temp. 103.4°	O	Unkn.	Unkn.
7-11	None	O	+	+
7-14	Chills, temp. 101.4°	O	Unkn.	Unkn.
7-20	Chill, temp. 103°, hemoglobinuria	O	+	+
7-22	None	O	+	+
8- 3	None	O	−	−
8-11	None	O	−	−
8-17	None	O	−	−
8-23	None	O	−	−

One week following a transfusion (July 22) a warm agglutinin was detected in the serum of Patient H which was tested with 127 known bloods of all groups.* When the figures were corrected for the frequency of the Rh factor in the population at large (85%), the reactions corresponded closely with a serum first described by Levine *et al.*[2] and designated as anti-Rh_1 by Wiener, Sonn and Belkin.[12] This antibody is characterized by the fact that it agglutinates the blood of approximately 70% of white individuals of New York City and by the fact that it clumps a small number of bloods (Rh′) which fail to agglutinate with standard anti-Rh serums. The serum from Patient H agglutinated 69% (corrected figure) of the bloods tested. Among these were 5 individuals characterized as Rh negative with the standard 85% serum obtained from Dr. Levine.

The second patient, Z, was a white male, age 22, admitted to this hospital Nov. 15, 1943, with a diagnosis of aplastic anemia. At other stations he had received a total of 5 transfusions from October 5 to November 10 without reaction. At this hospital, between January 3 and March 15, he received 10 transfusions, at least 5 of which were Rh-positive bloods. Only minor reactions were noted. On July 8 his anemia became more pronounced and transfusion therapy was again resumed after an interval of nearly 4 months. In the next 4 days he had severe reactions to only small quantities of blood, sub-

* The A and B substance of Witebsky, used to inactivate the isohemagglutinins, was obtained through the generosity of the Eli Lilly Company.

sequently found to be Rh positive (Table 2). At the same time the recipient was tested and found to be Rh negative. However, we were unable to demonstrate Rh antibodies in his serum and cross-tests with known Rh-positive cells were thoroughly compatible *in vitro* at 37° and at ice-box temperature. Nevertheless we proceeded to give him only Rh-negative blood on empiric grounds. From July 13 to August 8 he received 13 transfusions with only 2 minor febrile reactions. During this period the patient's serum was investigated for the presence of atypical antibodies without success. Since our supply of Rh-negative donors was limited and since we had no actual proof that the Rh factor was involved,* it was decided to attempt once more an infusion with

TABLE 2.—TRANSFUSIONS, PATIENT Z

Date	Reaction	Donor's group	Type Rh
1– 3	None	A	+
1– 7	None	A	–
1–12	Chill, 101°	A	+
1–26	None	A	+
2– 2	None	A	–
2– 8	None	A	Unkn.
2–15	None	A	Unkn.
2–22	None	A	+
3– 4	None	A	Unkn.
3–15	Chill, 102°	A	+
7– 8	250 cc., chill, vomiting, 102.8°	A	+
7–11	175 cc., chill, 101.6°	A	+
7–12	200 cc., chill, 102°	A	+
7–13	None	O	–
7–14	None	O	–
7–15	None	O	–
7–19	None	A	–
7–20	101.6°	A	–
7–21	None	A	–
7–22	None	A	–
7–24	101.2°	A	–
7–25	None	A	–
7–26	None	A	–
7–27	None	A	–
8– 5	None	A	–
8– 8	None	A	–
8–11	Vomiting, jaundice, hemoglobinuria, 104.6°	A	+
8–16	None	A	–
8–22	None	A	–
8–23	None	A	–
8–24	None	A	–

Rh-positive blood. Transfusion was started at approximately 3:30 P.M. on Aug. 11, 1944; when 200 cc. had been infused, signs of beginning reaction became evident in the form of headache, nausea and malaise. These symptoms grew progressively more severe, until the headache was intense and vomiting occurred. The transfusion (500 cc.) was completed at about 6:00 P.M., at which time the patient was found to have a temperature of 104.8° F., although he stated that he did not feel especially warm and had had no real chills. Later in the evening the patient appeared markedly toxic and weak and experienced severe

* There was some suspicion of pyrogens in transfusion sets at that time.

bouts of nausea and vomiting. On the following morning icterus was apparent (icterus index 64) and his urine contained some red cells and a large amount of free hemoglobin. Alkalies and fluids were promptly administered and a satisfactory output of urine was obtained. The icterus diminished rapidly and the hemoglobinuria disappeared within 24 hours. The hemorrhagic phenomena and underlying thrombocytopenia were apparently little affected by the transfusion reaction.

A specimen of blood from this patient was examined only 4 hours after transfusion and we were unable to demonstrate the presence of the Rh-positive cells. Similar negative results were obtained the following day. This observation was not surprising in view of the subsequent serologic findings and the rapidity with which jaundice and hemoglobinuria developed. The patient's serum was then tested for "blocking antibodies" of the type recently reported by both Wiener[7] and Race.[3] Z's serum, 0.2 cc. of varying dilutions, was incubated for 1 hour at 37° C. with 1 drop of a 2% suspension of Rh-positive cells. One drop of an appropriate dilution of anti-Rh serum was then added to each tube; the mixtures were again incubated for 1 hour at 37° C. and examined for agglutination. Appropriate control sera from negative unsensitized individuals failed to inhibit the Rh agglutination reaction.

TABLE 3.—Rh BLOCKING TEST—PATIENT Z'S SERUM

	Date 1944	Dilutions of serum									
		15	20	30	40	60	80	120	160	240	320
1	8– 5	–	–	–	–	–	–	–	++	++	++
2	8– 8	–	–	–	–	–	–	–	++	++	++
3	8–11*	–	–	–	–	+	++	++	++	++	++
4	8–12	–	–	–	–	+	++	++	++	++	++
5	8–14	–	–	–	–	++	++	++	++	++	++
6	8–16	–	–	–	–	–	–	–	++	++	++
7	8–19	–	–	–	–	–	–	–	+	++	++
8	8–23	–	–	–	–	–	–	–	++	++	++

* Serum obtained 4 hours after transfusion with Rh positive blood.

It should be noted (Table 3) that 6 days prior to transfusion the serum of Patient Z contained Rh-inhibiting antibodies to a titer of 1:120. Four hours following transfusion (August 11) and for 3 days thereafter the titer was reduced to 1:60; this in turn was followed by a subsequent restoration to the former level (August 16). At no time were agglutinating antibodies demonstrable in the patient's serum. The drop in titer following infusion of Rh-positive blood was regarded as evidence of the union of donor cells and antibody *in vivo*.

Discussion. Patient H in whom agglutinating antibodies of Type Rh_1 were demonstrable, exhibited several characteristic features of acquired iso-immunization. A succession of transfusions was required before evidences of transfusion reaction appeared and these became progressively more pronounced, finally terminating in frank hemoglobinuria. As Wiener has pointed out, hemolysis due to Rh incompatibility may be at first not apparent but may eventually result in a severe or fatal reaction.[6] Appropriate examinations of blood from

Patient H, utilizing the factors M and N as an index of the destruction of donor cells, may have aided us in avoiding the acute reaction of July 20 and the risk of serious outcome.[6,11] The development of symptoms probably due to the Rh factor within a month after the initial transfusion is a shorter time than usually required for iso-immunization. However, Vogel, Rosenthal and Levine[4] reported a case (No. 4) in which only 8 transfusions and an interval of $1\frac{1}{4}$ months was adequate for the development of anti-Rh agglutinins.

The specificity of the antibody in Patient H is of some interest inasmuch as its relationship to the Rh factor was at first obscured by the fact that it reacted with some Rh-negative bloods.[2] A serum giving somewhat similar reactions was also reported by Wiener[5] from a case involving multiple transfusions and subsequently classified as anti-Rh_1 by Wiener and Landsteiner.[10] It is of interest to note that the blood cells of all Rh-positive donors tested (Table 1) were agglutinated by the serum of Patient H, indicating that they belonged to the sub-types Rh_1 or Rh_1Rh_2.[12] On the basis of the distribution of the Rh_1 type which occurs in 50%, in contrast to the Rh_2 type which is found in only 15.5% of the general population, it is to be expected that the anti-Rh_1 iso-immunization would occur more frequently than the anti-Rh_2. Only recently Waller, Levine and Garrow reported a case of erythroblastosis fetalis involving the Rh_1 factor in which the mother of the baby was Rh_2.[5] Additional cases of iso-immunization of Rh-positive mothers of Type Rh′ have been described by Levine, Burnham, Katzin and Vogel,[2] and by Wiener.*[8]

The second patient, Z, is also of special interest because of the high titer of Rh blocking antibodies present in his serum despite the absence of demonstrable agglutinating antibodies. This finding confirms the observation of Wiener[7] regarding the development of inhibiting (non-agglutinating) factors in sera of patients sensitized to the Rh antigen. Since only 2% of Rh-negative individuals respond by producing agglutinins to the Rh factor following multiple transfusions,[9] the demonstration of an inhibiting antibody is of considerable value as a method of detecting Rh sensitization where agglutinating antibodies are not present in the circulation.[4,6] We have recently had the opportunity to apply the blocking test in 2 cases of iso-immunization during pregnancy which resulted in erythroblastotic infants. Both mothers were Rh negative and the fathers Rh positive. Interval tests during the period following delivery failed to reveal the presence of Rh agglutinins. Blocking antibodies, however, were present in a titer of 1:2 in 1 case and 1:16 in the other. One additional case is worthy of mention. This patient was an O, Rh-negative male with suppurative pulmonary disease who received 24 transfusions over a period of $1\frac{1}{2}$ years with no reactions whatsoever. On Aug. 17, 1944, two 500 cc. transfusions using O, Rh-positive donors were given with benefit and without reaction. One month later the recipient's serum was tested but Rh agglutinins were not demonstrable. Tests for blocking antibody, however, were positive to a titer of 1:4. In view

* See for additional references.

of the above findings this patient, although sensitized to the Rh factor, was apparently able for some unknown reason, to receive Rh-positive blood with impunity.

Summary. Two cases of severe reactions following multiple transfusions were found to be due to the Rh factor. In 1 patient an atypical agglutinin conforming to the sub-type Rh_1 was demonstrable. In the second, the Rh antigen was implicated by finding a high titer of "blocking" antibodies in the recipient's serum despite the absence of agglutinins.

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THE ACCEPTABILITY AND EFFECTIVENESS OF THE CONDOM AS A CONTRACEPTIVE METHOD*†

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INSTRUCTION in contraception has an important place in any complete public health program. Its importance in cases where pregnancy is contraindicated is well recognized. Of almost equal importance is its use to prevent unduly frequent pregnancies with their unfavorable effect upon mother and child. While the diaphragm-and-jelly method is considered very reliable, its general introduction in the public health

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field has been limited by the amount of the physician's time required for fitting and the details of instruction. For this reason the simpler methods are capable of much wider application. Of these, only foam-powder-and-sponge[2,3] and jelly-alone[4,5,6,9] have been widely studied.

Technical improvements of the past decade have produced condoms which, being thinner and more carefully inspected for holes and other defects than previously, interfere less with sensation during intercourse, are more durable, and promise a higher degree of protection than earlier sheaths. *A priori* they would seem well adapted to use in public health programs. They have not, however, been tested on a large scale in a controlled experiment.

To secure an estimate of the acceptability and effectiveness of condoms under conditions closely resembling those of a public health program, a series of carefully studied cases were planned by Dr. Gilbert W. Beebe under the auspices of the National Committee on Maternal Health. Condoms of an assured high quality (Trojans) were supplied by the Youngs Rubber Corporation. They had been tested by the manufacturer by being mechanically stretched over a blunt metal cylinder whose diameter was 1.5 times that of the condoms when flaccid. When dipped in a solution of a neutral wetting agent, holes were indicated by a ring of fluid beneath the rubber, and any such condom was rejected. This technique appeared superior to the earlier practices of inflation and visual inspection. Because of it and in order to keep the procedure as simple as possible, further testing by the user was not suggested.

A rural area where the population had been little exposed to education in matters of birth control was found in Watauga County, N. C. To make the results applicable to situations where little or no physician's time would be available, the physician in charge (J. B. H.), after choosing the patients in need of pregnancy spacing, directed a registered nurse, Lena Gilliam Hillard, R.N., to give the instructions. She was peculiarly well-fitted for the work, being a native of a similar region in Kentucky and having assisted at Berea in a test of the acceptability and effectiveness of jelly-alone.[5] As the work progressed it became evident that the families for whom the physician had prescribed the service comprised a major portion of the rural farm population. Therefore, in order to approach the statistically desirable ideal of an unselected population, he instructed the nurse to offer the same service to all couples.

As the county contained more rural-farm families than could be included in the program, representative geographical selection was secured by subdividing it into 26 areas bounded by roads, and choosing 13 of these at random. Although service was given to a few colored couples, the present analysis has been limited to whites to secure a more homogeneous material. To avoid inclusion of a large number of women past menopause, those above the age of 45 years were likewise eliminated. The population studied, accordingly, comprises all the married white rural-farm women under 45, living in the 13 areas constituting approximately half of Watauga County.

At the first visit the need for birth control was discussed with the wife and the use of the condoms explained. If the free supply of these was accepted, a dozen condoms were left. Those who accepted the service were revisited 2 weeks later. If at this visit the condoms had not proved satisfactory, the nurse was instructed to make suggestions for better use of the sheaths, such as the use of a lubricant. If it was found that both wife and husband were satisfied with the method, a larger supply was given and further follow-up visits were made at intervals of about 6 months. Repeated use of each sheath was not suggested.

The history taken at the initial visit provided a record, as accurate as the patient's memory permitted, of the exposure to pregnancy and of the use or non-use of contraception for each month of her married life, as well as of each pregnancy and its termination. At every follow-up visit this information was brought up to date. All patients were followed until they decided to abandon the service or until they left the county. The present analysis covers the first 4 years of the project, from its onset in September 1939 to late in 1943. During the later part of this period a certain proportion of the follow-up work with the more intelligent and coöperative patients was carried out at the nurse's office in Boone or by mail.

Although a considerable number of women became accustomed to write for supplies, it should be clearly understood that the main initiative and responsibility for the continuation of the service rested at all times with the physician and the nurse. For many of the participants the service remained something which was brought to them without effort on their part rather than something they went out of their way to obtain.

A total of 658 married couples were found in the survey area who fulfilled the conditions listed above. The mean age of the wives was 29.3 years, the mean duration of marriage 10.3 years. The occupation of 83% of the husbands was recorded as farmer, the others being a miscellaneous group, including laborers, mill workers, carpenters, mechanics, mail carriers, storekeepers, and a few teachers and ministers. Of the families, 17% had received some relief during the year. The median number of school years completed was 7.8 for the husbands and 8 for the wives. The average number of children ever born per marriage was 3.2. Contraceptive techniques (including withdrawal) had been used by 45% of all couples, and were being used at the time of the interview by 38%. Of the 249 couples practicing contraception, 65% were using condoms, 17% withdrawal, 5% douches, with jellies, suppositories, safe period and diaphragm, each accounting for 2% or less.

Human fecundity and the efforts to control it are most adequately studied in terms of pregnancy rates "per 100 years of exposure." For this purpose the duration of exposure is computed by deducting from the total months of married life under consideration those during which conception cannot occur because of pregnancy, abstinence, separation and the like. The pregnancy rate per 100 couples per year

of exposure or, for conciseness, per 100 years of exposure, is calculated by the formula:

$$\text{Pregnancy rate} = \frac{\text{Total number of conceptions}}{\text{Total months of exposure}} \times 1200$$

It is necessary to distinguish periods of exposure without and with resort to contraception. The pregnancy rate per 100 years of exposure is higher for the period before the first pregnancy than afterwards, because later exposure includes months of postpartum amenorrhea and lactation during which the risk of pregnancy is reduced. Previous investigators have reported rates from 112 to 271 for first pregnancies and from 70 to 105 for second and subsequent pregnancies, when no contraception was used.

Since the majority of studies of his type have been made in connection with birth control clinics, the terms "pre-clinic" and "post-clinic" have come into general use. For this reason they will be employed here, although no clinic in the conventional sense was operated in Watauga County and the terms "pre-interview" and "post-interview" perhaps would be technically more correct. During the pre-clinic period, while no contraception was being used, those who accepted supplies had a pregnancy rate of 125 per 100 years of exposure for first pregnancies and of 64 for later pregnancies. That their untutored efforts at birth control had been effective is shown by a rate of only 13 pregnancies per 100 years of exposure for periods when contraception was used after the termination of the first pregnancy.

From the point of view of usefulness in public health work, the acceptability of a method is of great importance. The first measure of this, the proportion of those to whom condoms are offered who will try them, depends on many imponderable elements, such as the personality of the individual making the offer, the religious background and educational status of the couples, their previous experience with the condom or other contraceptive methods, and many others. For the couples who were already using condoms at the time of the first interview, the proportion who accepted the supplies was understandably high, amounting to 91%. For those who were using other methods and for those not using contraception, the proportions were almost identical, being 49 and 48% respectively, and 59% for all wives interviewed. Of the 271 refusing the service, 28% felt they did not need it because of natural or operative sterility. Twenty-five per cent stated they had religious or moral objections and 13% wanted a baby as soon as possible.

An even more important measure of acceptability is the proportion of those who accepted and tried the supplies who were still using condoms after varying lengths of time. This proportion amounted to 85, 79 and 73% after 1, 2 and 3 years, surprisingly high figures in view of the current clinical opinion that the male will not long tolerate the interference with sensation. The proportions were somewhat higher, as may be expected, for those who were using condoms at the time of the first interview, lower for those who were not practicing

contraception at that time, and lowest for those using other methods, being 81, 71 and 61% respectively, at the end of 3 years.

Taken as a whole, the acceptability of the condom in terms of continued use seems to be relatively high in comparison with the published findings for other contraceptives.[2,5,6,10] This comparison, however, can only be made in a general way because of the differences in investigative technique. Furthermore, the readiness with which couples may obtain materials and instruction for other methods varies from group to group. It should also be emphasized that the high ratios of continued use were obtained under the stimulus of home visits by the nurse at regular intervals. It seems probable that a mode of distribution requiring greater initiative and effort from the participants would have been less successful.

As might be expected, the complaint of "interference with sensation" was the most frequent one given as a reason for discontinuing the use of condoms. Among couples who stopped in spite of continuing exposure to the risk of pregnancy, this reason was recorded in two-fifths of the classifiable cases. In 44 instances the discontinuance could be definitely attributed to one of the spouses, 38 times to the husband and 6 times to the wife.

The post-clinic pregnancy rate shows a marked reduction from that before the patients had been given condoms. In a total of 649 years of exposure to the risk of pregnancy, 72 conceptions occurred, corresponding to a rate of 11 per 100 years. The same rate was found when first pregnancies were left out of consideration. This includes all unplanned conceptions before the method had been definitely and permanently discontinued, even those occurring after the patient had run out of supplies or after other irregular use. To determine the rate which would have resulted had the method been used according to instructions on every occasion is impossible, because it is evident from the records that irregular use was in many instances only admitted after conception had taken place. An approach to the appraisal of "physiologic effectiveness" is suggested by the fact that irregular use was admitted for three-fourths of the unplanned conceptions, and even more by the observation that of pregnancies terminated prior to the closing of the records, four-fifths were followed by resumption of condom use. Ten of the pregnancies were alleged to have followed an occasion on which the condom was found to have broken. In only 9 cases of unplanned pregnancy out of the total of 72 was perfect use on every occasion claimed.

Those with previous experience in some form of birth control were found to be more successful in limiting conceptions after receiving condoms, having a post-clinic rate of 6 second-and-subsequent pregnancies per 100 years of exposure compared with one of 16 for those who had never previously practiced contraception.

Comparisons with the physiologic effectiveness of other methods are difficult, since no two populations can be assumed to have the same degree of skill and regularity in the use of a method. The results secured in Watauga County, when compared with other reports

(Table 1), show that, under conditions of actual use, the effectiveness of the condom surpassed that of jelly-alone and of foam powder-and-sponge and almost reached that of diaphragm and jelly. When the rate of 6 for those with previous contraceptive experience is considered, it is seen to equal the lowest rate previously reported, one secured with diaphragm and jelly in a private practice composed chiefly of college-trained women from upper-middle-class homes.[8]

TABLE 1.—COMPARISON OF PREGNANCY RATES PER 100 YEARS OF EXPOSURE* DURING USE OF CLINICALLY PRESCRIBED CONTRACEPTIVES

Method and residence	Years of exposure	Pregnancies	
		No.	Rate
Diaphragm and jelly:			
Philadelphia[5]	935	59	6
Port Chester, N. Y.[1]	472	32	7
New York City[10]	703	65	9
Cincinnati[10]	2703	244	9
Nashville[2]	361	32	9
Spartanburg, S. C.[10]	671	87	13
Condom:			
Watauga County	604	68	11
Foam powder-and-sponge:			
Urban Florida[7]	377	103	27
Nashville[2]	206	57	28
New York City[11]	82	29	35
Jelly-alone:			
Philadelphia[4]	60	9	15
New York City[7]	203	33	16
Chicago[9]	241	47	20
Rural Kentucky[5]	204	41	20
Logan County[6]	938	354	38

* Chiefly for second and subsequent pregnancies.

Since the acceptability and effectiveness of condoms were found to exceed those indicated by current clinical opinion, it would appear that this contraceptive method is capable of much wider application in the public health field than has hitherto been made. The time required for instruction is short and this portion of the consultation can be delegated to a nurse. Although the method is primarily one for the use of the husband, it has been shown that instruction can be given satisfactorily through the wife.

Summary and Conclusion. 1. Under conditions closely resembling those of a public health program, condoms were offered by a registered nurse, under the supervision of a physician, to married women requiring pregnancy spacing. Subsequently the service was extended to include all married women living on farms in half of Watauga County, N. C.

2. Supplies were accepted and used by 59% of the couples.

3. Of those who tried the condoms, 73% were still using them after 36 months.

4. The post-clinic pregnancy rate was 11 per 100 years of exposure, including cases of irregular use. The protection approximated that reported for diaphragm-and-jelly and exceeded that afforded by foam powder-and-sponge and by jelly-alone.

5. The prescription of condoms for the prevention of dangerous or undesirable pregnancies requires little of the physician's time and is well suited to inclusion in public health programs.

A more detailed review of the findings appears elsewhere.[12]

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THE MAGNESIUM PARTITION IN HYPERTHYROIDISM

With Special Reference to the Effect of Thiouracil

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Serum magnesium is only partially ultrafiltrable in normal persons. In human blood, by ultrafiltration, Watchorn and McCance[17] found that the diffusible magnesium varied between 60 and 90% with an average of 80% ±7. Recently Soffer and his associates[13,15] have noted in Graves' disease that, although the total serum magnesium was normal, the non-diffusible, or bound magnesium, was much increased at the expense of the diffusible fraction. Administration of Lugol's solution to the patient caused a decrease in the bound magnesium while thyroidectomy restored the levels of diffusible and non-diffusible magnesium to the normal range. In myxedema the situation was found to be reversed, all the magnesium being in the diffusible fraction. Dine and Lavietes[5] confirmed these findings and suggested a possible relation of bound magnesium to the thyroid hormone or to certain enzyme systems.

Cope and Wolff[4] reported that they were unable to find consistent differences between the levels of the bound magnesium of hyper-

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thyroid patients and normal individuals. They likewise reported that the effects of iodine administration and thyroidectomy on the bound serum magnesium were equivocal.

Thiouracil has been found effective in the treatment of hyperthyroidism.[1,18,19] This drug acts by preventing the synthesis of the thyroid hormone. While investigating the action of thiouracil in relation to various electrolytes, its effect on the serum magnesium partition was studied.

Methods. Blood was drawn under oil from subjects in the postabsorptive state. Serum was separated as soon as adequate clotting had occurred, since hemolysis introduces serious errors into the determination of the magnesium fractions.[12] Serum was usually ultrafiltered as soon as obtained. Otherwise, it was stored under oil or paraffin at 5° C. Ultrafiltrates were obtained by an anaërobic technique, employing the capsule of Lavietes.[7] A "450" washed cellophane membrane was employed, with an effective ultrafiltration pressure of 28 cm. mercury. All ultrafiltrations were carried out for 8 to 12 hours at room temperature. An average of 4 cc. of ultrafiltrate was obtained from about 10 cc. of serum. The total serum magnesium was determined on 2 cc. amounts of serum by the method of Briggs.[2] Calcium was precipitated by the method of Clark and Collip.[3] Phosphate was determined colorimetrically by the method of Tschopp and Tschopp.[16] Ultrafiltrable magnesium was determined as was the total serum magnesium except that the protein precipitation of the ultrafiltrate with trichloracetic acid was omitted. Known amounts of magnesium sulfate equivalent to 1 mg. % magnesium were carried through with each set of determinations to insure the accuracy of the method. Bound magnesium was expressed as the arithmetical difference between the total and ultrafiltrable magnesium levels. Total serum protein was determined by the copper sulfate method.[10]

TABLE 1.—TOTAL SERUM MAGNESIUM AND THE PER CENT OF NON-DIFFUSIBLE (BOUND) MAGNESIUM IN NORMAL INDIVIDUALS

No.	Sex	Total serum magnesium (mg. per 100 cc.)	% of bound magnesium	Total protein (gm. per 100 cc.)
1	M	1.91	17	5.8
2	M	2.06	26	6.0
3	M	2.16	27	5.8
4	M	2.60	32	5.3
5	M	2.31	30	5.8
6	M	2.22	25	
7	M	2.24	36	6.0
8	M	2.55	32	
9	M	2.65	35	
10	F	2.32	42	
11	F	2.01	29	
12	F	2.06	17	5.7
13	F	2.16	31	5.8
14	F	2.21	40	5.8
15	F	2.15	29	
16	F	2.30	36	5.5
17	F	2.68	34	
18	F	2.36	29	
	Mean:	2.28 ± 0.03	30.4 ± 1.1	

Results. Total and ultrafiltrable magnesium determinations were made in normal individuals, and in patients with hyperthyroidism before and during treatment with thiouracil.

Table 1 shows the results obtained in 18 normal persons, chiefly internes and technicians. There were 9 males and 9 females in the

TABLE 2.—THE TOTAL AND PER CENT OF NON-DIFFUSIBLE (BOUND) MAGNESIUM IN PATIENTS WITH HYPERTHYROIDISM; THE EFFECTS OF THIOURACIL

								Thiouracil administered											
								1 week			2 weeks			3 weeks			4 weeks or longer		
No.	Sex	Age	Duration of illness (mo.)	Total protein (gm. p. 100 cc.	Initial BMR	Total serum Mg (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg (mg./ 100 cc.)	% bound Mg
1	F	43	12	5.5	+48	2.08	30	+43	2.03	25	..	..	..	+16	2.11	25	+17	1.61	30
2	F	20	12	5.8	+60	1.59	25	+33	2.29*	40	+33	1.95	22	..	..	..	+11	2.36	35
3	F	42	18	4.9	+53	1.67	30	+37	1.84	27	0	2.06	22						
4	F	34	24	5.5	+56	2.04	26	+33	1.91	25	..	..	..	+12	2.29	23			
5	F	35	12	5.5	+51	1.94	36	..	..	..	+30	2.08	29	..	..	..	+12	2.08	17
6†	F	35	48	5.5	+41	1.03	47	..	..	..	..	..	..	+19	1.00	36			
7‡	F	60	6	..	+77	2.18	44	..	..	..	..	2.12	31						
8	F	54	36	5.1	+96	2.79	52	..	2.21	7	..	..	..	..	..	..	..	2.24	21
9	F	28	12	5.2	+65	2.11	10	..	..	..	+30	1.62	11	..	..	..	+11	1.94	27
10	F	28	3	8.5	+33	1.74	26	..	..	..	..	..	..	−24	1.81	20			
11	F	31	8	..	+35	1.08	9	..	..	..	+35	1.37	27						
12	F	46	5	6.4	+40	1.37	28	..	..	..	+11	1.59	9	..	..	..	−2	2.04	35
13	M	38	12	5.3	+34	1.96	25	..	..	..	..	..	..	..	..	..	+20	2.28	31
14	M	35	12	5.5	+60	1.48	14	..	..	..	..	1.93	26						
15	F	22	5	..	+50	1.22	44												
16	F	26	12	5.2	+64	1.67	17												
17	F	21	6	6.5	+68	2.16	36												
18	F	51	12	..	+56	1.91	23												
19	F	56	24	5.6	+52	1.54	5												
20	F	28	5	5.2	+63	2.16	43												
21	F	50	6	6.0	+57	2.06	43												
22	F	54	12	5.3	+50	2.21	31												
23	F	54	10	5.5	+52	1.98	31												
24	M	42	24	..	+58	2.92	58												
					Mean:	1.87 ± 0.06	30.5 ± 1.9												

* Slight hemolysis.
† These patients received iodine at some time during their illness, but not for a considerable period before their treatment with thiouracil was started.
‡ This patient had received Lugol's solution for about 60 days previous to therapy, but had shown no good response.

group, with ages ranging from 20 to 35 years. Total serum magnesium varied between 1.91 and 2.68 mg. per 100 cc. with an average of 2.28 ± 0.03 mg. per 100 cc. Ultrafiltrable magnesium ranged from 1.33 to 1.76 mg. per 100 cc., with a mean value of 1.58 ± 0.02 mg. per 100 cc. The percentage of non-diffusible magnesium varied from 17 to 42%, with an average of 30.4 ± 1.1%.

Table 2 shows the results obtained in 24 cases of hyperthyroidism. There were 20 females and 4 males, varying in age from 21 to 60 years. The total serum magnesium varied from 1.03 to 2.92 mg. per 100 cc., with an average of 1.87 ± 0.06 mg. per 100 cc. The ultrafiltrable magnesium ranged from 0.55 to 1.90 mg. per 100 cc., with an average of 1.28 ± 0.03 mg. per 100 cc. The percentage of non-diffusible magnesium varied from 5 to 58%, with an average of 30.5 ± 1.9%.

Table 2 shows also the effect of thiouracil administration in 14 cases of hyperthyroidism. The thiouracil* was given in daily doses of 0.6 gm. for 2 weeks, followed by daily doses of 0.4 gm. until the basal rate was approximately normal, when a maintenance dose of 0.1 to 0.2 gm. daily was given. Those patients in whom specimens were obtained after 3 weeks or more of such therapy all had undergone a remarkable clinical improvement and were gaining weight. Unfortunately, in 4 patients, levels could not be determined after 14 days of treatment because of surgical intervention or other causes.

Although the percentage of non-diffusible magnesium decreased to some extent in 6 patients (3, 5, 6, 7, 8, 10), in the remainder it was not either appreciably affected or actually rose.

TABLE 3.—A COMPARISON OF THE EFFECT OF THIOURACIL ON THE PERCENTAGE OF NON-DIFFUSIBLE (BOUND) MAGNESIUM OF SERUM AND THE BOUND IODINE OF PLASMA

Days of treatment	BMR	Bound magnesium (mg. per 100 cc.)	% of bound magnesium	Bound iodine (μg. per 100 cc. of plasma)
0	+60	0.39	25	14.7
7	+33	1.36*	40	11.4
14	+33	1.53	22	7.2
28	+12	1.53	35	5.6

* Slight hemolysis.

Table 3 shows the decrease in plasma bound iodine in patient No. 2 Table 2) while receiving thiouracil, as contrasted with the negative effect on the level of the percentage of non-diffusible magnesium.

Comment. Our data show the average total, diffusible, and non-diffusible serum magnesium levels of hyperthyroid patients to be slightly lower than the comparative average values for normals. The average value for the percentage of non-diffusible magnesium is almost identical in the two groups, however. The range of the percentage of bound magnesium in hyperthyroidism is strikingly varied, being just twice as great as the range for normal individuals.

It is interesting that our data differs from that of Soffer *et al.* and Dine and Lavietes, not so much in the average values obtained in hyperthyroid patients, as in the higher average percentage of bound

* Thiouracil (Deracil) was kindly supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.

magnesium found in normal individuals. Our data resembles that of Cope and Wolff more closely, although their average percentage of bound magnesium for both thyrotoxic patients and normals is somewhat higher than we obtained. The average values for the total, the ultrafiltrable, and the bound magnesium which these latter observers obtained in hyperthyroid patients are almost identical with our own. Examination of Soffer's data[15] shows that 22 of his 50 cases of hyperthyroidism had less than 30% of the total serum magnesium in the non-diffusible fraction, and he has recently reëmphasized the fact[12] that the percentage of bound magnesium is not elevated in all cases of thyrotoxicosis.

It is generally accepted that there is an excessive amount of circulating thyroid hormone in thyrotoxicosis. One of the best indices of this increase is the protein-bound iodine level of the plasma, which has been found consistently elevated in hyperthyroidism.[11] It has been found that thiouracil causes a decrease to normal of the basal metabolic rate and the plasma protein-bound iodine in thyrotoxicosis.[18] In 1 case treated with thiouracil (Table 3) in which simultaneous iodine and magnesium determinations were obtained, there was no correlation between the two levels.

The effect of thiouracil on the absolute value of non-diffusible magnesium, and the percentage of the total serum magnesium which was non-diffusible, was quite inconstant. These data would seem to suggest that magnesium probably does not represent part of the thyroid hormone *per se*. Soffer has noted[13] that injections of thyroglobulin into dogs causes a rise in the bound magnesium, but only after some time has elapsed. The injection of thyroxin into dogs has no appreciable effect on the magnesium fraction.[14] This again suggests that magnesium is probably not an integral part of the thyroid hormone.

Thyrotoxicosis causes profound alterations in most, if not all, the metabolic processes of the body. Magnesium is known to be necessary for the activity of certain enzyme and co-enzyme systems.[6,9] One of the best recognized of these is the pyruvate oxidation system which also requires the presence of diphosphothiamine. It is known that persons with thyrotoxicosis are deficient in diphosphothiamine, and have high pyruvic acid blood levels.[20] This is but one of the many metabolic alterations in thyrotoxicosis which might explain wide fluctuations in non-diffusible magnesium in this disease. The amount of protein in the diet influences the absorption of magnesium from the gastro-intestinal tract[8] which must also be considered in an evaluation of the magnesium partition. In view of these and many other factors which must influence such an important ion as magnesium, it appears that the magnesium partition will have to be studied in a greater number of metabolic disturbances before its significance in hyperthyroidism may be evaluated.

Summary. 1. Diffusible and non-diffusible serum magnesium fractions were determined in 24 hyperthyroid and 18 normal persons. In the thyrotoxic cases the non-diffusible fraction ranged between 5 and 58% of the total serum magnesium, with an average of 30.5 ± 1.9%.

In normals the non-diffusible fraction varied from 17 to 42% of the total, with an average of 30.4 ± 1.1%. Thus we have been unable to demonstrate significant increases in the percentage of the non-diffusible fraction of the total magnesium in hyperthyroidism.

2. Thiouracil apparently has no constant effect on the magnesium fractions in hyperthyroidism.

3. It is suggested that the variability in the magnesium fractions in thyrotoxicosis is the reflection of alterations in metabolic processes.

The author wishes to thank Dr. Robert H. Williams for valuable advice in the conduct of this study, and Dr. Roger S. Hubbard for statistical analyses of the results.

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VITAMIN LEVELS IN SPRUE*

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Most authorities agree that sprue is due to "a profound disturbance of the power of the intestines to absorb in a normal fashion the products

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of digestion,"[5] and should be classified as a deficiency disease. However, the rôle of vitamin deficiencies in the production of the disease is still a controversial matter. For example, it has been reported that the glossitis of sprue will subside following the administration of nicotinic acid.[7] Others[8] have found that nicotinic acid is of no value whatever.

In the past few years, laboratory tests have been devised for the determination of the levels of various vitamins and are now fairly well standardized. By applying these laboratory methods to patients having sprue, one should be able to measure the levels or degrees of saturation of the various vitamins. This might make possible a more exact study of this disease and enable one to determine with reasonable accuracy what vitamin or vitamins are depleted in a given patient. In this communication the vitamin levels of 12 patients having sprue are reported.

Material. The 12 cases of sprue reported here were selected with the greatest care, on the basis of steatorrhea, glossitis, macrocytic hyperchromic anemia, flat glucose tolerance curve, and marked weight loss. Two of the patients had previously been diagnosed as having sprue, according to the criteria stated above, but were in remission at the time of this study.

For the purpose of comparison, a second group consisting of 25 patients who wered diagnosed clinically as having a mild or early vitamin deficiency of the B-complex was selected. These patients were of the same economic level as that of the group having sprue and so far as could be ascertained were subsisting upon essentially the same diet. A control group of 30 normal medical students also was studied.

Method. The method of study was similar to that described in a previous communication.[12] To summarize, all patients were hospitalized and given a standard diet, low in vitamins, but adequate in proteins and calories. The control group of 30 medical students was given this diet during the period of study but allowed to continue their usual activities. The following laboratory tests for vitamins were carried out: Vitamin C was measured in the Evelyn photoelectric colorimeter, using Tillman's dye and the technique of Mindlin and Butler.[9] Vitamin A determinations were made by the method of Kimble.[6] The vitamins of the B-complex were determined in the urine before and after the following test doses: thiamin, 1 mg. i.m.; riboflavin, 5 mg. orally; nicotinic acid amide, 500 mg. orally; pyridoxine, 50 mg. orally. Thiamin was determined at first by the yeast fermentation technique of Atkin, Schultz and Frey[1] which includes the total thiamin and pyrimidine fractions, and later by a modification of the thiochrome method.[3] Riboflavin was measured by the direct fluorometric method of Ferrebee,[4] omitting the adsorption and elution steps. The nicotinic acid load-test was based on the previous study of Perlzweig, Sarett and Margolis.[10] Values for F_2 determined fluorometrically[11] paralleled closely those for total nicotinic acid excretion. Pyridoxine was determined colorimetrically by the technique of Scudi *et al.*,[13] including the form hydrolyzed by heating with acid.

Results. The vitamin levels in the 3 groups, as determined by the procedures described above, were compared and are shown in the accompanying tables and charts. The "suggested lower limit of normal" as shown in the accompanying charts was based upon a previously reported study.[2]

Vitamin A. The plasma levels of vitamin A in the 30 normal students show a distribution and a mean well above those of the 25 patients having vitamin deficiencies (Chart I). It is important to

TABLE 1.—ARITHMETICAL MEANS OF VITAMIN LEVELS

Vitamins	30 Student controls	25 B complex deficiencies	12 Sprue	Suggested lower limit of normal
A	115.0	89	48	75
Carotene	265.0	205	49	165
C	0.67	0.33	0.06	0.15
Nicotinic acid	88	48	57	65
Thiamin: Control period	672	455	260	400
Load-test	415	150	156	300
Riboflavin: Control period	810	490	280	400
Load-test	3300	2100	1630	2200
Pyridoxine	7.0	5.2	5.8	4.7

Vitamin A—international units per 100 cc. of plasma.
Carotene—international units per 100 cc. of plasma.
Vitamin C—mg. per 100 cc. of plasma.
Nicotinic acid—urinary excretion in mg. in 14 hrs. after test dose of 500 mg. orally.
Thiamin: Control period—urinary excretion in gamma in 24 hrs.
Load test—urinary excretion in gamma in 4 hrs. after 1 mg. intramuscularly.
Riboflavin: Control period—urinary excretion in gamma in 24 hrs.
Load test—urinary excretion in gamma in 24 hrs. after 5 mg. orally.
Pyridoxine—urinary excretion in mg. in 4 hrs. after 50 mg. orally.

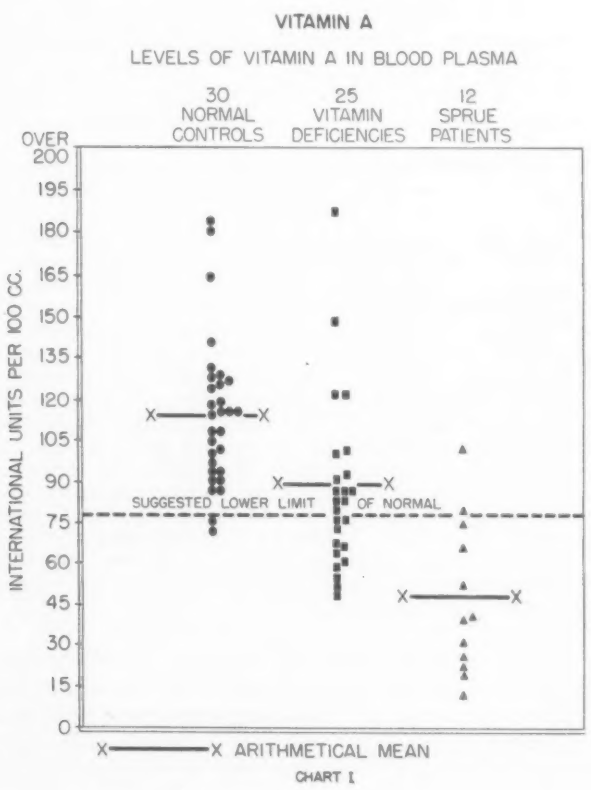

CHART I

note that the values in the 12 patients having sprue were likewise much lower than those of the deficiency group (Table 1). Nothing to suggest a vitamin A deficiency clinically was observed in any of these patients.

Carotene. The general distribution of values for plasma carotene between the three groups was the same as that in vitamin A, yet the difference between the mean in those patients having sprue and those of the other groups is even more marked (Chart II).

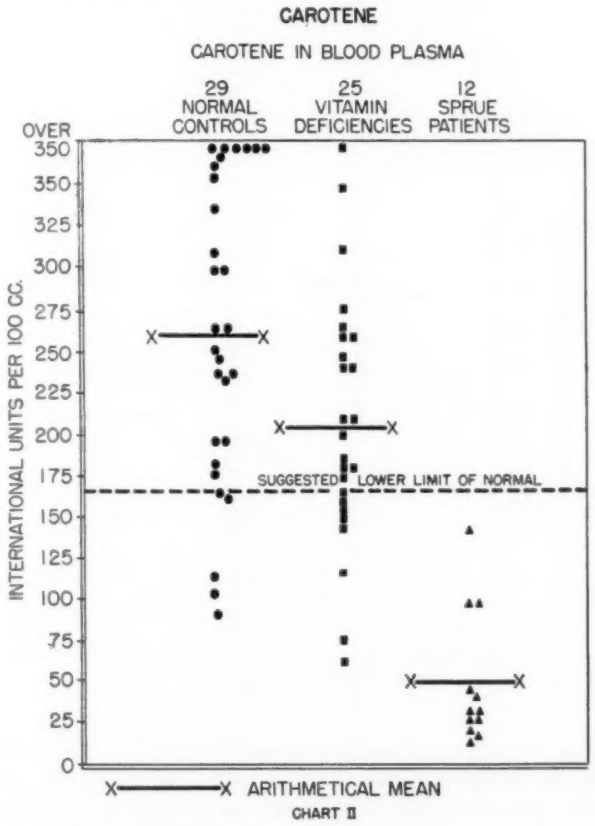

CHART II

Vitamin C. While there were individuals in each group whose plasma contained no measurable vitamin C, still over half of the patients having sprue had levels of zero, and the remainder were below 0.3 mg. per 100 cc. (Table 1). None of the patients showed any clinical evidence of scurvy.

Nicotinic Acid. A comparison of the urinary excretion of nicotinic acid in the three groups, following the administration of 500 mg., is of interest. It will be noted that the mean of the patients having sprue is somewhat higher than that of the deficiency group, but both were considerably lower than the normal controls (Chart III).

Riboflavin. The distribution of values of the urinary excretion of riboflavin, both during the control period and after the oral administration of 5 mg. in the 3 groups, is shown in Charts IV and V. The mean of the patients having sprue was definitely lower than that of the patients classified as having a vitamin deficiency and both were significantly lower than that of the normal control group.

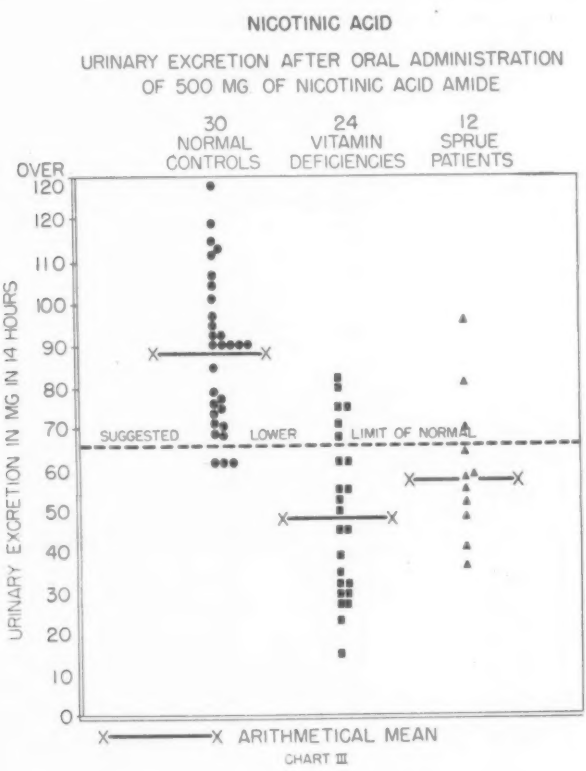

CHART III

Thiamin. During the control period of thiamin excretion, the distribution of values between groups was essentially the same as in riboflavin. However, after the intramuscular administration of 1 mg. of thiamin, the means of the excretion levels were the same in those patients having sprue as in those having a vitamin deficiency, although both were well below that of the normal control group (Table 1).

Pyridoxine. There were no significant differences in distribution or mean values of the 3 groups in the urinary excretion of pyridoxine, after the oral administration of 50 mg. (Table 1).

Discussion. It is generally recognized that single deficiencies are rarely if ever seen clinically. In sprue with the anorexia which regularly accompanies the disease, the diarrhea and interference with intestinal absorption, one would naturally expect multiple vitamin deficiencies to be present. The findings in this study confirm this

impression. One notes that patients with sprue are apt to have low values for the B-complex and vitamin C. This is especially true of thiamin and riboflavin. However, the nicotinic acid levels in the patients with sprue were a little above those of the 24 patients classified clinically as having a vitamin deficiency. A possible explanation of this finding might lie in the fact that in sprue there is marked wasting with destruction of body tissues, and this would afford a certain amount of nicotinic acid for utilization by the body.

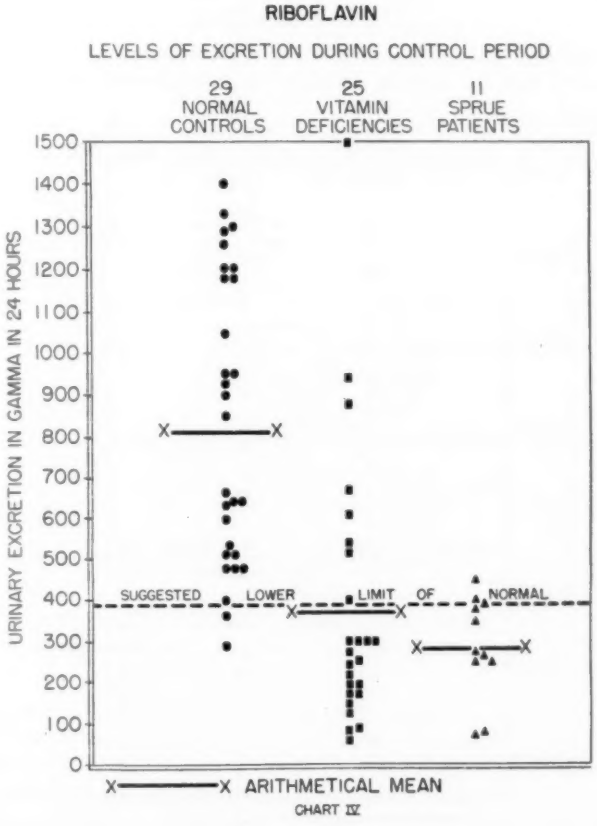

CHART IX

The striking difference, however, between the sprue patients and the patients having clinically a B-complex deficiency is in the vitamin A and carotene levels. Here we see that the plasma level of vitamin A is much lower than in the deficiency group and that the depletion of carotene in the blood plasma is even more striking. This is to be expected, since it is known that fats are poorly absorbed in sprue, and vitamin A and carotene being fat-soluble are lost as a result. It might be suggested that the diarrhea alone is responsible for these low levels. However, a comparison with patients having amebic dysentery shows that such is not the case. The mean of the plasma

vitamin A in 8 patients having amebic dysentery was found to be 91 international units, which is within normal limits, and almost twice that of the sprue patients, which was found to be 50 I.U. The same marked difference is noted in the carotene levels. In the 8 patients having amebic dysentery the mean was 141 I.U. as compared with a mean of 50 I.U. in the sprue group. This would suggest that carotene is absorbed chiefly in the small intestine. Likewise there is a striking difference between the carotene and vitamin A levels in sprue as compared

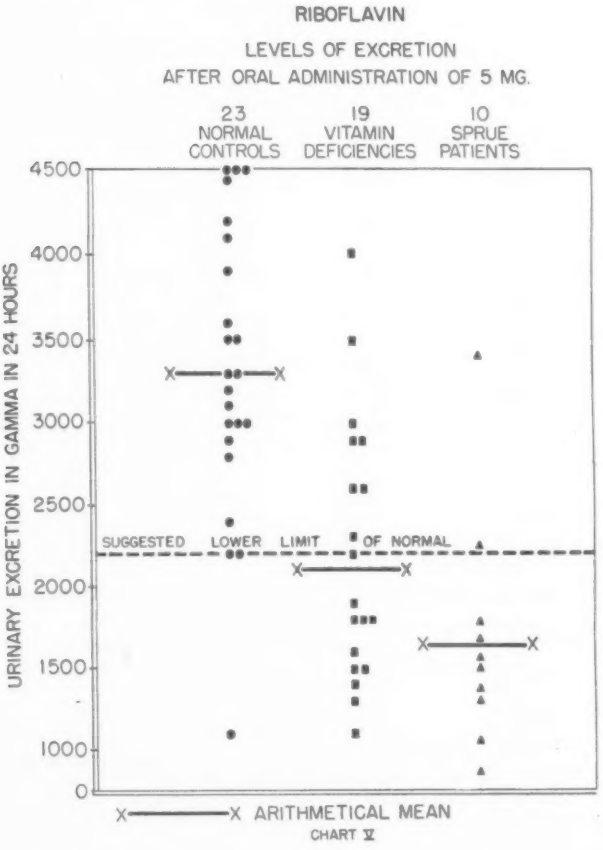

CHART V

with those in pernicious anemia. In 8 patients having pernicious anemia, the mean for vitamin A was found to be 83 I.U. and that of carotene 154 I.U. as compared with a mean of 50 I.U. in both vitamin A and carotene in the sprue group. The determinations of plasma vitamin A and carotene are relatively simple procedures and can be carried out in any well-equipped laboratory. The striking differences in the distribution and means of vitamin A and carotene suggest that these determinations may prove helpful not only as an aid in the diagnosis of sprue, but also in distinguishing it from pernicious anemia.

Conclusions. 1. Multiple deficiences of the B-complex are the rule in patients having sprue.

2. The plasma levels of vitamin A and carotene in patients having sprue are significantly lower than the levels of normal individuals, as well as those of patients who have clinical evidence of a B-complex deficiency.

3. The determination of the plasma levels of vitamin A and of carotene is a useful laboratory procedure in the recognition of sprue.

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EARLY FILARIASIS (BANCROFTI) IN AMERICAN SOLDIERS*

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Filariasis (bancrofti) is a widespread disease occurring in tropical and subtropical countries of both the eastern and western hemispheres. It is prevalent in the Pacific Islands, southern Asia, Africa, the West Indies, and along the northern coast of South America.

Our present concept of the disease begins with the discovery of microfilariæ in the hydrocele fluid of a resident of Cuba by Demarquay (see Belding[2]) in 1863. In 1866, Wucherer recovered microfilariæ from chylous urine and 10 years later Bancroft isolated an adult worm from a lymphatic associated with a filarial lesion of the arm. In 1878, Manson described the life cycle of the filaria with the mosquito acting as the intermediate host.[13] In more recent years, extensive studies have been made by Bahr,[1] O'Connor,[10] and Buxton[3] of the disease as it occurs in the Pacific islands. The early manifestations of filariasis,

* We regret the delay in publication of this article, which apparently left the hands of the authors last July and reached ours in March.—Editor.

as seen in the Armed Forces of the United States, have been described recently by Dickson *et al.*[4]

The Life Cycle of Wuchereria Bancrofti. *Wuchereria bancrofti* is a species of nematode (Order—Spirurida; Sub-order—Spirurina; Superfamily—Filarioidea; Family—Dipetalonematidea; Genus—Wuchereria).

Man is the only known definitive host. Microfilariæ circulate freely in the peripheral blood of certain infected persons. The intermediate host is a mosquito* which aspirates the microfilariæ† while sucking blood from an infected person. Metamorphosis takes place in the mosquito, being completed in a minimum of 8 to 9 days. During this time the larvæ have burrowed through the intestinal wall to the thoracic muscles, then to the proboscis where they are in the infective stage and from which they escape to a new definitive host. The mature larvæ break out of the tip of one or the other of the two labellæ which form the end of the labium.[7] They are probably incapable of penetrating normal skin but enter the subcutaneous tissues through the wound left by the mosquito. They enter the lymphatic where they mature into adult sexual forms. The maturation period takes from 3 to 12 months. The production of microfilariæ requires the fertilization of an adult female by an adult male. The microfilariæ thus produced enter the blood stream either by way of the thoracic duct or by penetrating the lymph spaces and entering the small vessels in the vicinity.

Clinical Syndrome. This series to be reported consists of 62 cases in which a diagnosis of filariasis bancrofti‡ was made. (Many more cases have been seen with symptoms and physical signs suggestive of such a diagnosis, but these cases are not included in the series.) All the patients reported were exposed to filariasis for 364 days.

The clinical cases may be divided into 5 groups (Table 1). The number and anatomic location of the lesions is shown in Charts 1 and 2. One or more case histories will be presented to demonstrate each group. Complete histories, and physical examinations were done but only the significant findings will be recorded. In the early cases demonstrating genital involvement, elaborate confidential questionnaires were prepared and repeated urine specimens and prostatic smears were examined to rule out venereal infection.

Case Abstracts. Case 1. Age 22. Eight months after leaving an island in the South Pacific, this patient noticed discomfort in his left testicle. This gradually became more severe and radiated up the left spermatic cord to the left groin. On the morning of the 3rd day after first noticing the pain, the left

* Although *Culex quinquefasciatus* (*Culex fatigans*) and *Aëdes scutellaris pseudoscutellaris* (*Aëdes variegatus*) are probably the most important, metamorphosis has been observed in at least 41 species of mosquitoes, including Anopheles and Mansonia.

† Investigators[2] have found that 3 microfilariæ per c.mm. will produce optimal infestation, that 0.5 will fail to infect, and that 10 will kill the mosquito. Bachman found that 84% of 565 *Culex fatigans* were infected with an average of 4 larvæ following a blood meal with a concentration of 1.75 microfilariæ per c.mm.

‡ It is assumed that the parasite concerned was *Wuchereria bancrofti*. The appearance of the microfilariæ and the fact that this species is endemic on the island where the troops were stationed substantiated this view.

"testicle" became swollen and the patient was admitted to the hospital. Examination of the genitalia revealed a definite thickening of the spermatic cord and a nodular, tender enlargement of the epididymis on the left side. The right and left inguinal and the left axillary lymph nodes were enlarged. On the 3rd day following admission, a hydrocele of moderate size was present. This gradually subsided. On the 4th day, there was edema of the scrotum. A painful and tender red streak was also visible in the left abdominal wall extending diagonally from the costal margin to a point just below and lateral to the umbilicus. The lymphangitis disappeared in 2 days but the scrotal edema persisted for 5 days. During his illness, this patient complained of pain radiating down the mesial aspect of the upper third of both thighs.

TABLE 1.—CLINICAL CLASSIFICATION OF EARLY FILARIASIS

Group	Clinical manifestations	No. of cases
I	Cases characterized by genital manifestations	47
II	Cases characterized by superficial lymphangitis of the extremities	13
III	Cases characterized by multiple lesions	16*
IV	Cases suggestive of involvement of the deep lymphatics	1†
V	Asymptomatic cases with microfilariæ in the blood	1
	Total:	62

* Not included in the total. When multiple lesions occurred, the first to appear is recorded in the group classification.

† This case is referred to elsewhere as "doubtful" but is included in the series to complete the clinical classification.

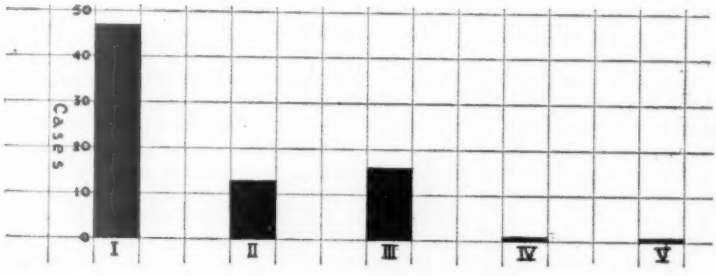

CHART 1.—Number of patients in each clinical group.

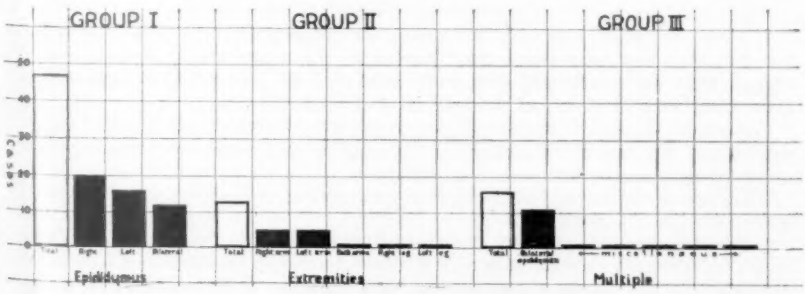

CHART 2.—Anatomic location of lesions by clinical groups.

At the time of evacuation from the combat zone 29 days after admission, slight thickening of the spermatic cord and epididymis was still present.

Laboratory Studies. Repeated urinalyses were negative; differential leukocyte count showed 6% eosinophils; venous blood concentrated and examined for microfilariæ was negative.

This case demonstrates the typical, mild genital involvement classified in Group I. In addition, it is the only case presented demonstrating multiple lesions (Group III).

CASE 2. Age 27. Four months after leaving the endemic area this soldier developed a pain in the left lower quadrant of the abdomen following heavy manual labor. During the night the pain radiated down the spermatic cord to the testicle. The next morning, swelling of the left "testicle" was noticed. Examination showed tenderness, and thickening of the left spermatic cord and epididymis. A small hydrocele was noticed. One large left inguinal lymph node was palpable. The pain continued. The hydrocele increased in size and was aspirated on the 3rd day for the relief of symptoms. After the 7th day, the pain subsided. The genital swelling decreased slowly until when last seen only slight thickening of the spermatic cord and epididymis remained.

Laboratory Studies. Repeated urinalyses were negative; differential leukocyte counts showed 7% eosinophils. Examination of the fluid aspirated from the hydrocele showed no microfilariæ. A microfilaria was found at 10:30 P.M. on the 3rd day of hospitalization, in the peripheral blood (cover-slip technique). Repeated examinations throughout 24-hour periods thereafter failed to demonstrate microfilariæ. This is the only case of the symptomatic cases showing microfilaria in the blood. The genital manifestations are typical of Group I.

CASE 3.—Age 25. Two months after leaving the endemic area, this soldier developed a pain in the mesial aspect of the right arm. He was admitted to the surgical service of the hospital with a diagnosis of acute lymphangitis—cause undetermined. No abrasion or infection could be found to account for the lesion. The right axillary lymph nodes were large and tender. Within a week the patient was well. Six months later, the patient became aware of a painful and tender "lump" in the right axilla. The following day, pain radiated from the "lump" down the mesial aspect of the arm and within 24 hours a red streak was visible from the axilla to the midpoint of the anteromesial aspect of the arm. The patient was admitted to the hospital. On the 3rd day from the onset of the symptoms, examination revealed a diffuse swelling of the mesial aspect of the right arm. A red streak was visible. On palpation, a firm "cord" could be felt underlying the streak. There was increased local heat. The axillary lymph nodes were enlarged and tender. Three distinct nodes could be palpated. The patient could put his finger on the particular node which gave rise to his first symptom. The epitrochlear lymph nodes were palpable on both sides. Two days after admission, the right axillary lymph node indicated by the patient as the source of his pain was removed for biopsy. A live adult filaria was found in the node.

During the next week, the lymphangitis progressed distally to the wrist. By this time the signs previously present in the upper arm had disappeared except that the thickened lymphatic was still palpable. The patient was evacuated from the combat zone 17 days after admission.

Laboratory Studies. Repeated urinalyses were negative; differential leukocyte count showed 4% eosinophils. Repeated examinations of the capillary and venous blood failed to show microfilariæ.

This case is typical of Group II, but is the only one in which an adult filaria was recovered.

CASE 4. Age 23. Seven months after leaving the endemic area, this patient developed a dull aching pain in the right side of the abdomen associated with occasional twinges of pain in the right testicle. The pain gradually subsided. Three weeks later he developed severe pains in the right flank which radiated down to the anterior aspect of the right thigh. The pain was aggravated by rising from the supine to the sitting position. An aching pain radiated down the mesial aspect of both thighs when the patient walked short distances. Examination revealed tenderness below the right costovertebral

angle which extended laterally to the crest of the ileum. The entire right side of the abdomen was tender to deep pressure. There was questionable thickening of the right spermatic cord. Roentgen ray of the abdomen and lumbar spine was negative.

Laboratory Studies. Repeated urinalyses were negative; differential leukocyte count showed 4% eosinophils; no microfilariæ were found in the peripheral blood on repeated examinations.

This case is representative of a considerable number of "doubtful" cases suggestive of deep lymphatic involvement, referred to in Group IV. It is included to complete the clinical classification.

CASE 5.—Age 25. Five months after leaving the endemic area, this soldier developed a slight transient pain in the left testicle. Examinations by one of us at that time revealed a small varicocele on the left side. The wearing of a suspensory was advised and the pain was relieved. Three months later, microfilariæ were found in the peripheral blood during a survey of asymptomatic patients exposed to filariasis. Specific questioning revealed that for the past 3 days the soldier had noted a transient needle-like pain in the right testicle but it was so slight that he disregarded it. Examination of the genitalia was negative except for a varicocele on the left side. The right and left inguinal, the left axillary and the left epitrochlear lymph nodes were enlarged. The patient was hospitalized for observation. That night he noticed a dull aching pain in his right testicle, and the following afternoon it radiated up the spermatic cord to the right lower quadrant of the abdomen. Three days later he complained of a similar symptom in the left side. At this time the physical findings were not impressive but there was slight thickening of both spermatic cords. The pain in the right side disappeared promptly but persisted on the left side. Ten days later, definite thickening and induration of the left spermatic cord and epididymis could be demonstrated. The manifestations gradually subsided.

Laboratory Studies. Repeated urinalyses were negative; repeated differential leukocyte counts showed a mean eosinophilia of 7%. The results of smears taken for microfilaria are indicated in Table 2.

TABLE 2.—RESULTS OF EXAMINATION FOR MICROFILARIÆ IN CASE 5

1st day:	10 A.M. (survey)—9 microfilariæ per drop (cover glass technique)
	12 NOON—no microfilaria (conc. specimen)
	1 P.M.—no microfilaria (conc. specimen)
	3 P.M.—no microfilaria (conc. specimen)
	6 P.M.—no microfilaria (conc. specimen)
	9 P.M.—1 microfilaria per drop (conc. specimen)
	11 P.M.—no microfilaria (conc. specimen)
2nd day:	13 conc. specimens examined; all negative
3rd–6th days:	3 conc. specimens examined; all negative
7th–28th days:	1 conc. specimen examined; negative

This case represents Group V because at the time microfilariæ were found the patient had not complained of any discomfort and showed no positive physical manifestations.

Laboratory Studies. MATERIAL. On 50 of the 62 clinical cases presented, laboratory studies were fairly complete. These included complete blood counts, frequent differential leukocyte counts, examinations of the blood, aspirated fluids and urine for microfilariæ. Histopathologic and bacteriologic studies were performed on several lymph nodes. Bacteriologic studies were also made on aspirated fluids, blood and urine. Feces were examined for intestinal parasites and ova, the urine for chyluria. Skin tests were made on some patients. Examinations of the blood for microfilariæ and differential leukocyte counts were also made on 142 asymptomatic soldiers who were exposed to filariasis.

METHODS. 1. *Examination for Microfilariæ.* The technique found to be most satisfactory in searching for microfilariæ will be described in detail:

(*a*) Unconcentrated preparations are made by placing a drop of blood on a cover-slip; another cover-slip is superimposed and pressed gently until the blood is spread evenly on both slips. These are pulled apart quickly and placed blood down on a glass slide. They are examined as "wet" preparations under the low power objective. A moderately thin preparation will facilitate the finding of microfilariæ.

(*b*) Concentrated "wet" preparations are made by mixing 20 cc. of venous blood in a solution consisting of 100 cc. of 5% formalin, 5 cc. of 2% glacial acetic acid, and 1 cc. of 1% safranin. This is centrifuged for 2 hours. The supernatant fluid is removed and the residue examined as in (*a*). When a large number of specimens are to be examined, it is more convenient to concentrate only 2 cc. of blood in 10.5 cc. of fluid. These preparations keep well for several weeks.

(*c*) Stained thick smears are prepared by spreading a large drop of blood on a glass slide. The smears are dried for several hours and then laked in 0.01% saponin solution for 20 minutes. These are stained with diluted Wright's stain (1 cc. diluted with 45 cc. distilled water) for 1 hour. The smears are not washed or blotted. Concentrated sediment from urine and aspirated fluids are examined in the same way.

2. *Examination for Adult Filariæ.* A search was made for adult filariæ by gross, microscopic and roentgenographic examinations of lymph nodes and lymph vessels. The lymph nodes were either sectioned and gently teased apart under a hand lens, or were bisected and placed in normal saline solution at 40° C. Histopathologic sections of these nodes were examined. Roentgenograms for the detection of calcified adult filariæ were made in several instances.

3. *Skin Tests.* The technique of skin testing will be considered under the discussion of skin tests.

Positive Diagnostic Laboratory Observations. 1. *Microfilariæ.* Of 266 soldiers examined, only 2 were found with microfilariæ. Actually this represented over 2000 preparations examined at various periods during the day and night. Both were found on unconcentrated "cover-slip" preparations. Identification was made under the low power objective. On a "wet" preparation, the microfilariæ varied from 80 to 300 μ in length and 8 to 12 μ in width. They were gracefully curved, had bluntly rounded ends anteriorly, while the posterior third of the body tapered to a point. In 1 instance, an oscillating motion was observed within the sheath. This was not observed in others, although in some there was a sluggish bending motion of the posterior third of the body for a short time. On high power magnification several uniform, round, evenly spaced nuclei dispersed through the anterior three-fourths of the body were observed. Staining by Wright's stain was weak and only the nuclei were clearly defined.

2. *Adult filariæ.* Eight lymph nodes were examined for adult filariæ. In only 1 instance was a worm found. It was obtained by placing a bisected lymph node in normal saline solution at 40° C.; the live worm appeared on the cut surface of the gland. It was creamy white and smooth in appearance. Under the low power objective it was found to be curled on itself several times. It was estimated to be 30 mm. in length and 0.1 mm. in width. A bluntly rounded anterior end and a simple cylindrical esophagus could be identified.

Other Laboratory Observations. 1. *Hematologic Studies.* Red blood cell counts and hemoglobin were within normal limits. The average

leukocyte count was 6000 to 8000. The differential leukocyte counts were within normal limits except for eosinophils. An eosinophilia of 9% or more was considered abnormal.

In a survey of 509 soldiers studied at the hospital during a period of 8 months, all of whom had been stationed in the tropics 16 months or more, it was found that 269 (Group A) had been exposed* to filariasis and 240 (Group B) had been stationed on filarial-free islands. In Group A, 50 (18.5%) were found to have eosinophilia; in Group B, only 13 cases (5.4%) had this finding (Table 3). Group A was divided into Sub-group *a*—those with manifestations of filariasis, and Sub-group *b*—those who had no manifestations of filariasis. Analysis revealed that 33 (24.2%) of 136 soldiers constituting Sub-group *a* had eosinophilia, while 17 (12.7%) of 133 patients in Sub-group *b* had this finding. The per cent eosinophilia varied from 9 to 36% (Table 4). Sub-group *a* was further divided into Sub-group *a*–1, those with clinical filariasis, and Sub-group *a*–2, those with minimal or doubtful manifestations of the disease. Seven (14%) of the 50 cases constituting Sub-group *a*–1 had eosinophilia, whereas 26 (30.2%) of the 86 cases in Sub-group *a*–2 had this finding (Table 5). Chart 3 correlates graphically the findings outlined in Tables 3, 4 and 5.

TABLE 3.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS STATIONED IN THE TROPICS 16 MONTHS OR MORE

Group	No.	Cases with eosinophilia (9% or above)	eosinophilia (%)
A. Exposed to filariasis	269	50	18.5
B. Not exposed to filariasis	240	13	5.4

TABLE 4.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS EXPOSED TO FILARIASIS

Sub-group	No.	Eosinophilia	
		Cases	%
A. Soldiers with manifestations of filariasis	136	33	24.2
B. Soldiers without manifestations of filariasis	133	17	12.7

TABLE 5.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS WITH FILARIASIS

Sub-group	No.	Eosinophilia	
		Cases	%
a–1. With clinical filariasis	50	7	14.0
a–2. With minimal or doubtful filariasis	86	26	30.2

The above data suggest: the incidence of eosinophilia (9% or above) is significantly greater in soldiers exposed to filariasis as compared to those living in the tropics but not exposed to the disease. In exposed troops with manifestations of filariasis, the incidence of eosinophilia is greater than in those with no evidence of the disease. It is of interest that the incidence of eosinophilia in those with minimal or questionable filariasis was twice as great as in those with frank clinical manifestations of the disease.

* "Exposure" in this study implies continued residence in an endemic filarial area for 365 days.

2. *Histopathologic Examinations.* Eight lymph nodes and 2 hypertrophied lymphvessels removed from patients with filariasis were examined histologically. Some will be described in detail:

(*a*) PATIENT A. Patient noticed a painful swelling of his right arm which receded promptly. The right axillary and epitrochlear lymph nodes were enlarged. Differential leukocyte count revealed 3% eosinophils.

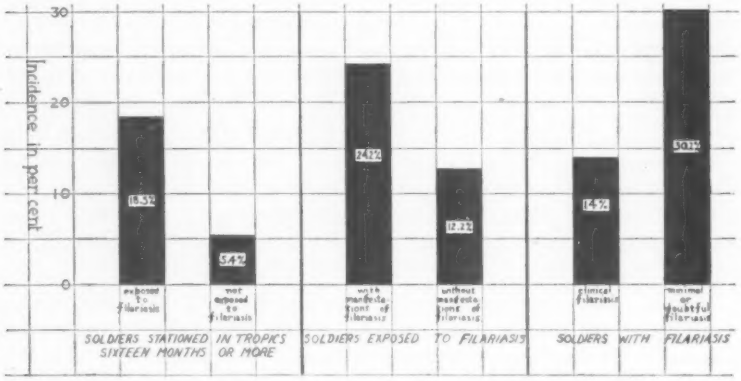

CHART 3.—The incidence of eosinophilia (9% or more).

The lymph node vessel removed for examination revealed an irregular mass of fibro-fatty tissue 0.8 x 0.5 x 0.3 cm. in size. Serial microscopic section showed multiple focal areas of necrosis were present. Some of these areas were hyalinized, filled with degenerating cellular débris and surrounded by neutrophils. The reticulum and lymph channels contained many eosinophils and neutrophils. The lymph vessel showed inflammatory thickening of the walls. *Impression:* acute focal lymphadenitis.

(*b*) PATIENT B. A few months prior to admission to the hospital the patient noticed enlarged left axillary lymph nodes. He was admitted because of pain and a swelling on the mesial side of his left arm. Within 2 days, redness, heat and swelling of the entire mesial aspect of the left arm and forearm were present. A red nodular palpable lymphatic extended from the axilla down the mesial side of the arm and across the antecubital fossa. The left epitrochlear lymph node was readily palpable. Differential leukocyte count revealed 8% eosinophils. After the acute process had subsided, the left epitrochlear lymph node and a portion of the lymphatic vessel were removed.

Gross examination revealed a discrete lymph node 1 x 0.5 x 0.4 cm. in size. The cut surface was grayish white and cellular in appearance. The lymphatic vessel was a thin fibro-fatty cord 6 cm. in length and 0.3 x 0.5 cm. in diameter along which were many small oval firm nodules. Histologic sections of the node revealed acute and subacute inflammatory changes, characterized by focal hyaline necrosis and diffuse eosinophilic infiltration through the reticulum. Neutrophilic infiltration, especially in the "pale centers," in some places was quite dense. There was edema, eosinophilic, plasma cell, and lymphocytic infiltration of the pericapsule. The lymphatic vessel showed inflammatory reaction and early fibroblastic proliferation. The attached lymph nodes were undergoing the same changes as the epitrochlear node. In addition, areas of early fibroblastic proliferation were present in these glands as well as the periglandular connective tissue. *Impression:* subacute lymphadenitis.

(*c*) PATIENT C. (Refer to Case 1.) A lymph node from the left inguinal region was removed for biopsy. Gross examination revealed a lymph node 1.5 x 1 x 0.5 cm. in size. The cut surface was grayish white and cellular.

Microscopic sections showed an inflammatory reaction characterized by diffuse infiltration of the reticulum with eosinophils which in some areas appeared in dense clumps. In other places the lymph sinuses contained many neutrophils. The lymphoid follicles and germinal centers were large and hyperplastic. The pericapsular connective tissue was edematous, infiltrated with many eosinophils and plasma cells and showed early fibrosis. *Impression:* subacute lymphadenitis with benign lymphoid hyperplasia.

(*d*) PATIENT D. This patient developed a painful swelling of the right epididymis and spermatic cord 3 months after leaving the endemic area. A firm nodule was palpable in the thickened spermatic cord about 2 inches proximal to the epididymis. The differential leukocyte count revealed 4% eosinophils. The nodule was removed for study.

Gross examination of the specimen revealed a lymph node 4 cm. in diameter. The cut section revealed a hard, slightly raised area measuring 4 mm. in length and 2 mm. in width. Roentgenograms of this node demonstrated a "comma-shaped" area of calcification. A broad zone of inflammatory reaction consisting mainly of epithelioid cells and Langhans giant cells surrounded the necrotic tissue. There was marked eosinophilic infiltration. Scarring, round cell infiltration, and increased vascularity were present at the periphery. A few dilated endothelial lined spaces, probably lymphatics, were seen. *Impression:* chronic granuloma with necrosis and calcification.

(*e*) PATIENT E. This patient was admitted to the hospital because of large, tender axillary lymph nodes on the right side. One node was removed for biopsy. At the same time a punch biopsy was taken from a right inguinal node. Four days later he developed acute centrifugal lymphangitis of the right arm which was associated with the development of a large discrete tender axillary node on the affected side.

Gross examination revealed a lymph node 1.2 x 0.8 x 0.5 cm. in size. The cut surface was pale and cellular. Microscopic examination was marked by infiltration of the reticulum and lymph sinuses with eosinophils, plasma cells and polymorphonuclear leukocytes. Focal areas of necrosis were present. The stroma was very vascular. There were isolated areas of fibroblastic proliferation and for the most part the lymphoid follicles were large and hyperplastic. *Impression:* subacute lymphadenitis with benign lymphoid hyperplasia.

Other investigators have had greater success in finding adult filaria in biopsied lymph nodes. Dickson[6] found filariæ in 6 of 14 lymphatic tissues from Marines with clinical filariasis. O'Connor[11] has stressed the eosinophilic infiltration and early fibroblastic proliferation seen in enlarged lymph node of patients with filariasis. This is not dependent on the presence of an adult filaria in the node but is probably allergic in nature.

Our findings are comparable to this description. Eosinophilic infiltration was the most constant finding. The additional findings of fibroblastic proliferation, focal necrosis and hyalinization further suggest that the changes are due to an allergin rather than a bacterial infection.

3. *Skin Tests.* In early cases of filariasis because microfilariæ are seldom found in the blood and the demonstration of adult filariæ is also difficult, the development of a satisfactory cutaneous test would be of great aid in the diagnosis of this disease. Fairley[5] has reported favorably on an intracutaneous test made from an extract of dog heart worm, *Dirofilaria immitis*, which is closely related to *W. bancrofti*. Mohr and Lippelt[9] have shown this test may also be positive in the presence of other nematodes. A complement-fixation test using an

extract of *Contortospiculum rheæ*, a filaria found in South America, may be more specific for filariasis. They report a small percentage of false positives. Dickson,[4] using an extract of the *D. immitis*, reports over 80% positive intracutaneous tests in patients with early filariasis and 4.7% positive tests in patients who have lived for several months in areas where filariasis is endemic. They described a positive test as one characterized by an immediate wheal reaching a diameter of 15 mm. or more, and by an edematous reaction occurring within 24 hours, measuring at least 20 mm. in diameter. Delayed reactions were recorded as doubtful.

As we were unable to obtain an extract of the Dirofilaria, an antigen* was made from an epitrochlear lymph node removed from a patient with filariasis manifested by superficial lymphangitis of the arm and who had an eosinophilia of 17%. No adult filaria was found in the node. The rationale for this was the possibility that allergy may play an important rôle in filariasis. It is reasonable to postulate that the allergen from the adult filaria may be present in sufficient concentrations in enlarged lymph nodes so that patients sensitive to a common allergin would react. Lippelt and Mohr[8] have shown that in Ascariasis, the antigen was derived from the products of metabolism of the worm, rather than from the worm itself. If this is true in filariasis, this test could be valuable, provided there is sufficient concentrations of "metabolic substances" in affected lymph nodes. The lymph node was digested with 0.6% pepsin in 0.3% hydrochloric acid at 37° C. for 12 hours. It was strained and diluted with an equal amount of normal saline solution and permitted to stand until the supernatant fluid was clear. This was removed and the residue treated with acetone and ether until a powder was obtained. It was preserved in a sufficient amount of 0.4% phenol in normal saline solution to make a 1:20 dilution. Eleven patients with clinical filariasis and 15 patients not exposed to the disease were tested by injecting 0.1 cc. of the solution intracutaneously. A control consisting only of menstruum was injected simultaneously. The test was considered positive when an erythematous wheal at least 0.5 cm. in diameter appeared within 36 hours. These positive reactions resembled a weakly positive Schick test. Of 11 patients with clinical filariasis, 7 (64%) showed positive reactions varying from 0.5 to 2 cm. in diameter. All controls were negative. There was no relation of the degree of eosinophilia to the intensity of the reaction. The intracutaneous reactions could in no way be compared to the reaction attributed to the extract of *D. immitis*. Because adult filariæ were not found in the gland, this experiment cannot be regarded as a specific test. However, it suggests that these patients were more or less sensitive to a common allergin present in an enlarged lymph node from a patient with early filariasis.

4. *Other Pertinent Data.* Repeated urine examinations for chyluria were done in all cases. Feces were examined to eliminate intestinal parasites as a cause for eosinophilia. Other common causes for

* This antigen was prepared by the method described by Sawitz for making Trichinella antigen.[1]

eosinophilia were excluded. Bacteriologic studies were done on biopsied lymph nodes and on aspirated fluid from lymph nodes, hydroceles, and a prepatellar bursa. Blood cultures and urine cultures were done on several patients. Pathogens were not obtained in any instance. The aspirated fluids were examined for microfilariæ but none were observed.

Discussion. It is to be kept in mind that this paper deals only with the early manifestations of filariasis. These lesions are due in some way to the presence of adult filariæ.

The manner in which adult filariæ produce the clinical manifestations is uncertain, but the following hypotheses deserve consideration: (1) Mechanical obstruction of lymphatics. (2) An allergic response to the living or dead adult filariæ or their products. (3) The discharge of microfilariæ by the fertilized adult female. (4) Secondary infection.

Bahr, Buxton and others have observed that microfilariæ disappear from the blood during an attack of acute lymphangitis. This has been demonstrated in clinical Case 5 of our series. If obstruction plays a part in this phenomenon, it follows that the adult filaria causing the obstruction is the one producing microfilariæ at that time. Although this may be the case in early or minimal infestation, it seems unlikely in advanced cases. Some of the lymph nodes and both of the lymph vessels which we removed for study showed fibroblastic proliferation and the lymph vessels were greatly thickened. This proliferative response to filariæ has been observed by Lane,[2] and could readily be a factor in obstruction. In addition the retrograde nature of the lesions suggest that there is some lymph stasis in the involved vessel. Contrary to the theory of obstruction, is the fact that in practically all parts of the body lymphatic anastomosis is very rich.

There is considerable evidence that allergy plays an important rôle. The very nature of the superficial lesions suggests an allergic response. The blotchy redness of the skin and the lack of severe constitutional manifestations in the presence of an acute inflammatory reaction are characteristic of allergy. The eosinophilic response as observed in the peripheral blood and the biopsied specimens is strong evidence in support of this theory. The allergin may be present in the living adult worms or be a product of their metabolism. The fact that many investigators, including ourselves, have found living worms in lymph nodes proximal to the affected parts, substantiates this. In contrast to this, O'Connor has shown that there is a more marked reaction around dead than living filariæ. The allergin may be produced by the disintegration of dead worms. No dead worms were found in this study. A high per cent of soldiers exposed to filariasis had eosinophilia. It is difficult to attribute their allergic response to dead filariæ because eosinophilia was observed also in those without manifestations. Eosinophilia was not present in all our clinical cases. The eosinophilic response to an allergin varies with the individual. In no disease in which eosinophilia is a characteristic response, would one expect to find it in every case.

That the acute manifestations of filariasis are not due to the sudden

release of large numbers of microfilariæ from the blood during acute attacks, and the fact that microfilariæ may be present in large numbers in the peripheral blood without causing symptoms, is sufficient evidence to cast grave doubt on such a theory.

The theory that the acute manifestations are caused by secondary bacterial infections is supported by the work of Grace,[6] who was successful in isolating beta-hemolytic streptococci in pure culture from the blood stream and the local lesions. The bacteriologic studies which we carried out, although incomplete, failed to demonstrate the presence of pathogenic organisms. It should be pointed out that the work of Grace and others regarding secondary infection has been done on natives, in whom the filarial infestation could be regarded as in a "late" stage. In such advanced cases, especially those with elephantoid lesions, secondary infection probably does play a part. Our studies suggest that the lymphangitis of early filariasis is an allergic response to a protein present in an adult filaria or a product of its metabolism. The response is manifest along a lymphatic which has been damaged or partially obstructed by adult filariæ or by the reaction to them.

The native term "mumu" is used extensively in the South Pacific Islands to describe both the acute lymphangitis described by Grace and the lymphangitis seen in early cases. The term is an ambiguous one that does not differentiate the bacterial from the bacteria-free lesions. The early lesions of filariasis are best demonstrated as they occur in clinical Group II. These lesions are superficial; the lymphatics are visible and drain into lymph nodes that are generally accessible for biopsy.

The manifestations depend on the location of the particular lymph node in which the adult filaria responsible for the reaction is located. Thus if the adult filaria is located in certain pelvic or peri-aortic lymph nodes, the genital manifestations of Group I result. If the worm is in a lymph node draining the superficial lymphatics of the extremities, the manifestations will be those of Group II. Similarly if the lymph node affected is one draining a deep lymph vessel where the reaction cannot be seen or felt, the diagnosis is not evident as in Group IV. The important fact is that the clinical manifestations will depend on the site of the node in which the adult filariæ causing the manifestations are located.

The clinical manifestations seen in Clinical Groups I and II are so typical and constant that the diagnosis on a clinical basis is seldom in doubt. The diagnostic criteria are outlined as follows:

a. Involvement of the Genitalia. 1. It frequently follows manual labor.

2. Testicular pain is the most common complaint.

3. The pain may radiate up the spermatic cord or may first appear in the lower quadrant of the abdomen and radiate down the spermatic cord to the testicle.*

* In 1 of our patients, right lower quadrant pain was present for 1 month before more definite manifestations were evident. A cigar-shaped tumor caused by the enlarged spermatic cord as it traversed the inguinal canal was seen the day prior to epididymal involvement. This demonstrates the centrifugal nature of the lesion.

4. The spermatic cord and epididymis are thickened and indurated.

5. An acute hydrocele is frequently present during the early stages.

6. Pain in the upper mesial aspect of the thigh on the affected side may be present.

7. Scrotal edema may also be present.

The most constant physical sign is the edema of the spermatic cord without involvement of the vas deferens. In the acute stages of the disease it is sometimes difficult to identify the structures of the cord on digital examination, but as the inflammation subsides, one is always able to demonstrate that the involvement does not affect the vas deferens.

b. Involvement of the Superficial Lymphatics of the Extremities. 1. Pain in the extremity radiating distally is the principal complaint. This pain may first be noticed in the proximal lymph nodes.

2. The extremity affected soon becomes edematous.

3. A definite "red streak" characteristic of acute lymphangiitis appears proximally. The affected lymphatic is palpable, and generally only a single vessel is involved.

4. There is increased local heat.

5. The lesion extends centrifugally.

6. Resolution begins proximally and also extends centrifugally.

7. The lymph glands draining the affected part are enlarged and tender.

8. Severe constitutional manifestations are absent.

9. There is no evidence of a focus of infection distally. In Group IV, the manifestations follow no definite pattern. In the majority of cases, as in Case 4, the diagnosis is presumptive. In any patient exposed to filariasis, one must be constantly on the alert for manifestations suggesting deep lymphatic involvement. By and large we have felt that the diagnosis of involvement of the retroperitoneal lymph nodes has been easier to recognize clinically than involvement of the deep lymphatics of the extremities. Pain in the flank or the abdomen, with radiation to the genitalia or the thigh is the principal complaint. Examination reveals tenderness of the abdomen on the affected side both anteriorly and posteriorly. In such cases it is necessary to rule out renal or ureteral disease which these findings may simulate. The only complaint in patients thought to have involvement of the deep lymphatics of the extremities is pain, with peripheral radiation. Slight swelling may or may not be present. The differential diagnosis includes skeletal, muscular and neurologic conditions. These are extremely difficult to rule out and in only few instances have we felt that this has been done to our entire satisfaction.

The absolute laboratory proof of filarial infestation depends upon the finding of either adult or microfilariæ. The difficulty of finding microfilariæ in these early cases cannot be overemphasized. Of 251 clinical cases reported by Dickson, in none were microfilariæ found. We were more fortunate in finding them in 2 instances (Cases 1 and 5).*

* The fact that only 1 microfilaria was observed in Case 1 left some doubt as to the significance of this finding. In Case 5, however, microfilariæ were observed on 2 occasions in appreciable numbers.

In order to find an appreciable number of microfilariæ in the peripheral blood, the total number present in the circulating blood must be enormous. When this occurs, it is probable that the microfilariæ are being produced by more than 1 adult female. We can assume that the degree of filarial infestation in our cases is slight because of the relatively short period of exposure compared to residents of endemic areas. Therefore, because the number of adults is dependent on the number of larvæ transmitted by the mosquito* and because the production of microfilariæ is further dependent on the fertilization of an adult female, the chances of microfilariæ being produced in these early mild cases are not great. Also, as the microfilariæ may disappear with the onset of clinical manifestations, the chances of finding them in the early clinical cases are lessened.

The finding of adult filariæ in lymph nodes has also been difficult in our cases. The lymphangitis of early filariasis characterized by centrifugal progression must be due to the presence of an adult filaria in a lymph node at the proximal end of the involved lymphatic. In clinical cases, where the involved lymph node is accessible for biopsy, it is imperative to select the correct node if one is to find filariæ. We believe that most of our biopsies were poorly selected. This probably accounts for the low incidence of adult worms recovered by us. In Case 3, the selection of the correct node for biopsy was obvious because the patient could put his finger on the axillary "lump" which caused his earliest symptom. In the remainder of the lymph nodes taken for biopsy (described under laboratory studies) a review of the histories and physical findings, suggests that in each case the node selected for biopsy was not the ideal one from which to recover filariæ. Although the recovery of adult filariæ is impractical where the involvement is deep, if one is careful in the selection of the lymph node for biopsy where the involvement is superficial, adult filariæ should be found in a high percentage of cases. The histopathologic findings in the lymph nodes and vessels removed by us had in common areas of subacute inflammation with eosinophilic infiltration and did not resemble the acute lymphadenitis caused by bacteria. This is a general eosinophilic response to an allergic process.

The incidence of eosinophilia as shown in Table 3 leaves little doubt that the soldiers exposed to filariasis had a significantly greater incidence of eosinophilia than those not exposed. This difference in the 2 groups is of even greater significance because over one-half of the soldiers in Group B (those not exposed to filariasis) were found to have systemic disease commonly associated with eosinophilia (cutaneous diseases, helminthiasis and so forth).

The breakdown of Group A (soldiers exposed to filariasis) into subgroups as shown in Tables 4 and 5 requires amplification. The 136 patients in Sub-group *a* include the patients seen with definite clinical

* The mortality of larvæ from the time they are deposited on the skin until they reach the lymphatics is great. The larvæ are lymphotactic. Lymph exuded at the site of the mosquito bite transmits the larvæ through the wound to the lymph spaces. Such a transmission is dependent on ideal conditions.

filariasis and also many others who had what is referred to in Subgroup *a*–2 as minimal or doubtful filariasis. The latter includes patients with such non-conclusive manifestations as vague testicular pain, history of recent previous swellings, vague pains in the extremities with or without swelling, slight thickening of the spermatic cord, small hydroceles, and generalized unexplained lymphadenopathy. Because these findings alone were inconclusive, the high incidence of eosinophilia assumes significance. As shown in Table 5, this subgroup had the highest incidence of eosinophilia. This finding may represent a greater allergic response during the earliest clinical stages of the disease. Subsequent observations on these patients after evacuations to a General Hospital[11] revealed that many of these patients developed typical clinical filariasis. In addition, skin tests done at this base, using an antigen made from *Dirofilaria immitis*, were positive in a majority of those exposed.

Epidemiology. The soldiers we observed were all exposed to filariasis for 364 days. Typical clinical manifestations of the disease were seen in over 11% of those exposed. It is difficult to estimate the probable rate of infestation. New clinical and doubtful cases are still appearing, even though the troops have been away from the endemic area for 8 months. It is not unlikely that the rate of infection is well in excess of 50%. Thus in endemic areas even though the period of exposure is relatively short, there is considerable danger of acquiring the disease. In our clinical cases, the percentage with microfilariæ is very small. As far as we know, no other investigators have reported the recovery of microfilariæ from such cases. It is conceivable, however, that many of these cases prior to the onset of clinical manifestations have had microfilariæ in their blood. Further observations are necessary to exclude the possibility of microfilariæ appearing at a later date.

Prognosis. The prognosis of these early mild filarial infestations cannot be definitely stated at this time. The local lesions are dependent on the number and location of adult filariæ. It is probable that only a small percentage of the adults present cause manifestations. The lymphangitis, although frequently recurrent, does not leave any demonstrable permanent damage as far as we have observed.

The end-result of extensive filarial infestations may be elephantiasis. However, even in the natives of endemic areas, the percentage that develop elephantiasis is very small. There is good evidence that such late manifestations are due to a secondary bacterial infection superimposed on a damaged lymphatic system.

In these early cases, therefore, when the exposure to filarial infestations has been relatively short and the damage to the lymphatic system minimal, the prognosis appears to be good. The adult filariæ present in the body may live for a number of years, but eventually die and become organized.

Psychosomatic manifestations have been reported by Rome and Fogel.[12] This was not a serious problem in the cases we observed. In retrospect, it is thought that this may have been avoided by individu-

ally reassuring those hospitalized and by instruction of all exposed troops by the commanding officer and the battalion surgeon. Emphasis was placed on the fact that no serious complication or permanent damage was likely to occur as a result of minimal filarial infection.

Prophylaxis and Treatment. Spread of the disease by early cases must be considered. Further observation is necessary to determine the extent of this problem. Until such time as more data are available, all soldiers with a history of exposure to the disease in an endemic area should be considered possible carriers.

Any troops going into filarial areas should have the advantage of specialized mosquito control. In addition, protection of the individual by the use of mosquito bars, head nets, leggings, long shirt sleeves, sprays and repellents is of great importance. Native villages should be "off limits" to all troops and natives prohibited from entering bivouac areas. Camp sites should be chosen as far removed from native villages as is practical.

Treatment of early filariasis consists of supportive measures. The lesions appear to be self-limited. During the acute stage, the patient should be hospitalized and the affected part put at rest. Mild analgesics are generally sufficient to control the discomfort. In some of our first cases the sulfonamide drugs were used but no change in the course of the disease was observed. Psychotherapy is essential in those patients who show undue concern regarding the final outcome of the disease. This has frequently been engendered by having seen natives with elephantiasis and by rumors of impotence and sterility.

Prevention of reinfection is an important aspect of treatment. Those with clinical manifestations and others similarly exposed should be observed in filaria-free areas with adequate mosquito control.

Summary and Conclusion. 1. A clinical diagnosis of early filariasis (bancrofti) has been made on 11% of a group of soldiers exposed to *Wuchereria bancrofti* on an island in the South Pacific for a period of 364 days.

2. The criteria on which a clinical diagnosis of early filariasis can be made has been outlined.

3. The diagnosis has been proved by the finding of adult and microfilariæ.

4. A clinical classification has been presented, based on the anatomic location of the lesion.

5. A high incidence of eosinophilia occurred. Eosinophilic infiltration and fibroblastic proliferation has also been noted in histopathologic studies.

6. We believe that the early manifestations are due to an allergin present in, or produced by, living adult filariæ and manifest along a lymphatic obstructed by the presence of, or the reaction to, the filariæ.

7. The clinical diagnosis is not dependent upon the finding of adult filariæ or microfilariæ.

8. Clinical manifestations may be multiple and are subject to recurrences.

9. The prognosis must be guarded but in the light of our present knowledge, it appears to be favorable if reinfection is prevented.

10. The clinical cases responded well to supportive therapy.

11. Some of the early cases may be carriers and rigid mosquito control should be carried out until more is known regarding the status of these patients.

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TULAREMIC PNEUMONIA

Review of American Literature and Report of 15 Additional Cases

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The marked increase in the number of reported cases of tularemic pneumonia in the past several years[11,23,37,47] indicates clearly that such frequent pulmonary involvement is additional evidence of the general-

ized, systemic nature of tularemic infections. In 1941, Blackford and Casey[11] found 150 reported cases of tularemic pneumonia in the American literature and added 12 additional cases of their own. Up to September 1944, we were able to collect 253 cases of tularemic pneumonia from the American literature. We propose herein to summarize the observations of 21 cases of tularemic pneumonia observed in the Charity Hospital of Louisiana at New Orleans. Six of these cases have been previously reported,[47,66] thus we are reporting 15 additional cases, bringing the total of collected cases of tularemic pneumonia in the American literature up to 268.

The first published reference to pleuropulmonary tularemia was apparently that reported by Verbrycke[65] in 1924, when he described in a patient dying of tularemia a number of nodules in the lungs, which were the size of hickory nuts and had the appearance of metastatic carcinoma, accompanied by a pleural effusion of 100 cc. Whitish nodules on the pleura and distributed throughout the lungs were observed in 1928 by Bardon and Berdez.[4] During the same year, Francis[25] called attention to the frequency of bronchopneumonia as a terminal event in cases of tularemia, and Simpson[56] suggested that the physical signs of consolidation in such cases might well be due to areas of caseous necrosis resulting from tularemia rather than to other types of bronchopneumonia. Likewise in 1928, Bunker and Smith[15] first recovered *Bacterium tularense* (*Pasteurella tularensis*) from the sputum. Massee,[43] in 1931, described a case of confluent pneumonia in which *B. tularense* was isolated. Permar and Maclachlan,[48] in the same year, described generalized areas of consolidation of a necrotic type which they called tularemic pneumonia. They expressed the opinion that necrosis had been produced by the extreme interstitial edema with monocytic infiltration and subsequent stenosis and thrombosis of the smaller veins and arteries. Also during 1931, Sante[55] described the roentgenographic findings of pleuropulmonary tularemia. Subsequent reports[3,5,9,10,12–14,16,19–22,24,28–31,33,34,41,46,49,51,58,59,61,64,67,68] of pleuropulmonary tularemia have been increasingly frequent.

Pathogenesis. That *B. tularense*, the organism which causes tularemia, is transmissible to man from animals has been well established.[57] Of the 268 cases of tularemic pneumonia available for study in the American literature (including 15 cases of our own), a definite history of contact with animals was available in 115 cases and may be summarized as follows: rabbits in 92 instances, ticks in 13, squirrels in 3, deerflies in 2, and woodchuck, opossum, cat, chicken hawk, and rat each in 1 case. In 2 additional cases, the probable source of infection was laboratory exposure in 1 instance and performance of an autopsy in another.

It is interesting to note that only 171 of the 268 patients (63.8%) had ulceroglandular, oculoglandular, or glandular types of the disease, whereas 97 cases (36.2%) had no demonstrable primary lesions or lymphadenopathy and may be classified, therefore, as the typhoidal type of infection. Foshay[23] observed that 52.2% of 46 typhoidal cases had pneumonia, while approximately 15% of 554 cases of other

types of tularemia developed evidences of pneumonia. Kavanaugh[37] found that 12.7% of his series of 123 patients had pneumonia. Similar figures were reported also by Blackford and Casey,[11] and Bihss and Berland.[6] It would appear, therefore, that pneumonia occurs most frequently in those cases without evidences of lymphadenopathy or primary lesions. Some appreciation concerning the incidence of typhoidal tularemia may be derived from the observation of Francis[26] to the effect that typhoidal tularemia represented 6.4% of 1856 collected cases.

Two schools of thought have sought to explain the mechanism by which *B. tularense* reaches the lungs: hematogenous dissemination and inhalation. Kavanaugh[37] and Simpson[56] favor the hematogenous point of view, as does the evidence submitted by Foshay[23] that there are two blood stream invasions, an initial one and a second bacteremia 5 or 6 days preceding death in many of the fatal cases. Permar and Maclachlan,[48] on the other hand, have suggested direct infection of the respiratory tract through inhalation and have discussed representative cases in which cutaneous ulceration and regional adenopathy were lacking. Bunker and Smith,[15] and others[32,47] have successfully recovered *B. tularense* from the sputum of patients with tularemic pneumonia. Recently, Aagaard[1] has reported the case of a graduate student in bacteriology who contracted tularemic pneumonia after an infected rabbit sneezed in the student's face. Several other laboratory workers have developed tularemia without presenting evidences of ulceration or regional adenopathy.[57] In 7 of 16 cases of Kavanaugh's series,[37] the infection appeared to originate as a primary pneumonia, suggesting that infection entered *via* the respiratory tract.

Comparative analysis of tularemia with other infections favors the inhalational method of infection. The similarities of tularemia to tuberculosis have been pointed out by Blackford,[7] while McCoy[45] referred to tularemia in animals as a "plague-like disease of rodents." Bihss and Berland[6] have recently discussed the clinical similarities between tularemic and bubonic plague. Reimann[53] states that the pathogenesis of primary pulmonic tularemia, like that of plague, is apparently inhalational in mode, such as inhaling bacilli suspended in the air as dust, in droplets from patients or animals who have tularemic pneumonia, or from handling dried cultures of the organisms.

Blackford and Casey[11] believe that infection through inhalation is rare if it does occur, and that failure to find the portal of entry does not mean that the organism entered *via* the respiratory tract. Eight of our 21 cases had no demonstrable portal of entry or evidences of regional lymphadenopathy. Historical data pertaining to these cases were, however, insufficient in most instances to determine whether or not inhalation of the organisms should be considered as the route of infection.

Morbid Anatomy. Blackford and Casey[11] found 56 necropsy reports of tularemia in the literature, but apparently overlooked Matthews' pathologic findings[44] of 3 patients who died from tularemic infection. Of the 56 autopsy records collected by Blackford and Casey,[11] lesions

of tularemic pneumonia were described in 35 cases, an incidence of 62.5% in fatal cases. Since Blackford and Casey's survey of the American literature, 39 additional necropsy reports[2,6,17,18,27,36,38,40,44,47,60,62,63,66,69] have appeared and lesions of tularemic pneumonia were described in 34 of these reports. It is evident, therefore, that of 95 patients who died of tularemia and who were subjected to postmortem examination, 69 presented lesions of tularemic pneumonia, an incidence of 72.6% in fatal cases.

Both the gross and the histologic features of tularemic pneumonia and tularemic pleural effusions have been discussed in detail by Lillie and Francis.[42] Recently, Blackford and Casey[11] reviewed the pathologic changes of pleuropulmonary tularemia and concluded that additional records of autopsies served only to verify previous observations. Although pneumonic involvement of the lungs is more frequent and more serious, an accompanying pleural reaction may be seen in about 50% of the cases of tularemic pneumonia. Thus, of 32 collected cases which proceeded to autopsy, Lillie and Francis[42] found pleural exudates in 16 cases and focal nodular lesions in the pleura in one other instance.

The most frequent pulmonic involvement in fatal cases is a lobular or confluent lobular form of pneumonia which may involve a single lobe, several, or all of the lobes. In cases with all the lobes involved, some lobes may contain only discrete nodules. It is not infrequent at postmortem examination to find lesions in all of the lobes. The usual phases of both gray and red hepatization are frequently found. The areas of gray hepatization present regions of central whitish or yellowish necrosis, which, on cut surface, not infrequently reveal small or large areas of coagulation or caseous necrosis and occasionally small, scattered, interseptal areas of focal necrosis. In some cases,[8] cavitation is present and may resemble those of chronic pulmonary tuberculosis. Pneumothorax, presumably resulting from a ruptured abscess, has been described.[37]

On microscopic examination, it will be found that the exudate is most frequently composed of mononuclear cells which are often phagocytic in character. A few lymphocytes, red cells, desquamated epithelial cells and plasma cells may be present. When secondary infection with the various cocci is superimposed, many neutrophils may be found in addition to the above reaction. The alveolar spaces are filled with a similar exudate which may contain fibrin at times. The alveolar septa are usually congested, especially in the pneumonic areas, and frequently the walls are necrotic. Interstitial infiltration by lymphocytes, mononuclear cells and other cells is not marked and is often confined to the interlobar septa, peribronchial and perivascular tissues. Some of the blood-vessels show mononuclear infiltration, necrosis and thrombosis.[48] The perivascular lymphatics may be distended with a cellular or caseous exudate. Lillie and Francis[42] found that the areas of focal necrosis in the lung apparently were simply necrosing pneumonic foci. According to some reports,[43] *B. tularense* have been seen in the lesions, but are rarely isolated or cultured from the pulmonic lesions as a general rule.

Symptoms. The symptoms presented by patients with tularemic pneumonia usually fall into two general groups: In the first group, the pneumonia is associated with the ulceroglandular, glandular, or oculoglandular types of tularemic infection and may occur from 1 or 2 days to many months after the localized infection elsewhere has developed. Thus, the symptoms of the pneumonia may occur with or follow the symptoms of tularemia elsewhere in the body, although the symptoms of pneumonia usually predominate in either case. In the second group, evidence of ulceration and lymphadenopathy is lacking. In these cases of typhoidal or cryptogenetic type of tularemia, the infection frequently appears to originate as a primary pneumonia, suggesting, therefore, that the infection may have entered through the respiratory tract. In this group, the onset may be sudden with a chill, fever, dyspnea, cough, pain in the chest and profuse sweating. The cough may or may not be productive. These patients appear extremely ill and are frequently suspected of having typhoid fever.

The pulmonary symptoms may vary greatly in severity. Frequently the symptoms are so mild that, without roentgenographic evidence, pneumonia cannot be recognized. In general, the pulmonary symptoms may be said to be less severe in character than those associated with other primary forms of pneumonia. Symptoms of bronchitis are usually present before pneumonia is recognized. Blackford and Casey[11] found cough present in 19 of 20 cases. Sputum was produced in only 50% of their patients; this varied in amount and occasionally was blood-tinged. Pleuritic or chest pain was experienced by 11 patients. Six patients were dyspneic.

The fever curve of tularemic pneumonia is usually irregular and spiking in nature, while the pulse rate is usually relatively slow in comparison, except for the tachycardia observed in the more severe or terminal cases. Rapid and shallow respirations, cyanosis, delirium, confusion or stupor, with rapid progress to a comatose state, may be observed in the most severe cases and, according to Foshay,[23] is frequently associated with a recurrent or secondary bacteremia.

Physical Findings. The physical signs of tularemic pneumonia vary with the type and distribution of lesions. Both lungs are frequently involved. In general, the physical findings are those of an atypical pneumonia. The patchy areas of consolidation are usually indicated by irregularly distributed and more or less circumscribed areas over which râles, bronchovesicular or bronchial breathing, and increased whispering pectoriloquy may be heard. These findings may vary in location and intensity from day to day. Occasionally, a lobar type of pneumonic consolidation may be demonstrated. Rarely, abscess cavities may be suspected in an occasional protracted case by the presence of amphoric breath sounds and "cracked-pot" resonance during percussion.

Physical examination of the chest may reveal no abnormal findings in some patients even though pleuropulmonary involvement can be demonstrated roentgenographically. Hence, roentgenographic studies of the chest of any patient with tularemia are advisable, since pulmo-

nary involvement in the form of an atypical pneumonia, with or without areas of focal necrosis, pleural effusion, nodular infiltration and peribronchial thickening is often found in the absence of significant physical findings.

Roentgenographic Diagnosis. In their patients with pleuropulmonary tularemia, Bihss and Berland[6] found that the most consistent Roentgen findings in the chest were enlarged and nodular hilar shadows, which usually occurred early in the disease. Frequently, these hilar shadows are not recognized as important until later accentuation of the lung markings radiating to the periphery have developed.

Bihss and Berland consider two basic types of pleuropulmonary involvement in tularemia. Non-typhoidal cases are thought to present usually hilar adenopathy in the early stages of the disease with subsequent retrograde extension through lymphatic channels into the lung parenchyma or even into the pleura with production of a pleural effusion. The second basic type is found in cases of typhoidal tularemia where the lung parenchyma is thought to be involved primarily and is usually not preceded by hilar adenopathy. The consolidations are large, homogeneous, and satisfy the roentgenographic criteria of pneumonia.

Abscess cavities are occasionally demonstrated roentgenographically in cases of pulmonic tularemia. Blackford and Casey[11] observed pneumothorax in 1 case and lobar atelectasis in another instance. Residual changes such as increased fibrosis are found in many cases.

Figures 1 to 4 show roentgenograms of the chests of 4 of our patients and have been selected to demonstrate the variety of roentgenographic findings seen.

Diagnosis. In typical cases of tularemia, the diagnosis of an accompanying pneumonia is not difficult if careful observations of the individual patient are made for evidences of pulmonic involvement, such as an increase in pulse rate, respiratory rate, fever, and the appearance of cough and sputum. Confirmation of the diagnosis should be made by roentgenographic studies. It is not possible, however, to be certain whether the pulmonary lesion is tularemic in nature or caused by a secondary infection with the wide variety of organisms normally present in the upper respiratory tract unless *B. tularense* can be demonstrated by bacteriologic methods.

In the typhoidal forms of tularemia, not only the pulmonic involvement must be demonstrated but the etiology of the underlying febrile state must be suspected and determined. In that connection the diagnosis of tularemia should be entertained in prolonged fevers of undetermined etiology. Moss and Weilbaecher[47] have reviewed the recent advances in the diagnosis of tularemia and have concluded that the diagnosis of a small percentage of cases, in which an occupational history, primary lesion, ulceration and lymphadenopathy are lacking, rests entirely upon the laboratory data, including the blood culture, agglutination tests, and animal inoculations. In their opinion, the blood culture is not generally reliable. Agglutination tests, especially if there is a rising titer, are of more value, but cannot be relied upon

until after the second week of the disease, and in fulminating infections may be delayed or may actually never develop throughout the entire course of the disease. Material secured by lung puncture or aspirated from the lymph nodes, blood and sputum may be inoculated into small animals with consistently reliable results. Likewise, tissues derived from the spleen, lung, lymph node and liver have been inoculated into small animals in order to establish the diagnosis of tularemia at post-mortem examination.

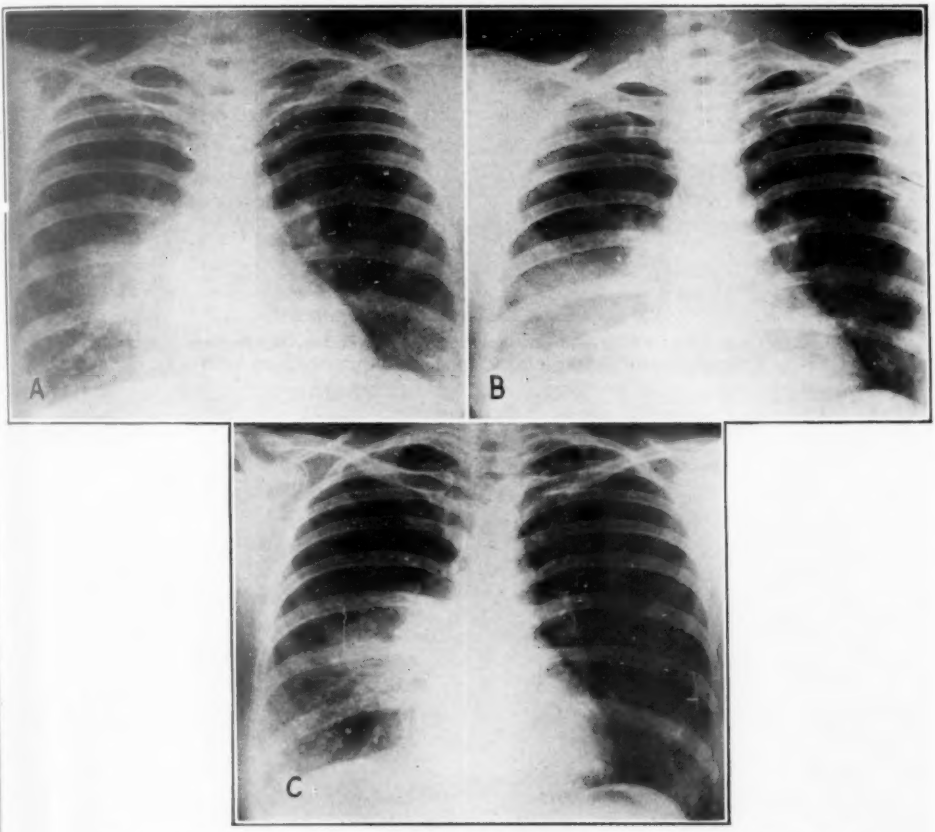

FIG. 1.—(Case 6.) The chest. *A*, On April 29, 1942, an opacity adjacent to lower pole of right hilum is clearly demarcated. Infiltration radiating from the hilum is seen. *B*, Four days later, the pneumonic consolidation has increased and extended to the periphery. *C*, On May 20, considerable resolution has occurred although a patchy, lobular involvement is still evident.

Other laboratory data are non-contributory to the diagnosis. The leukocyte count is usually within normal limits, although leukocytosis may occur infrequently. The red blood cell count is usually unaltered unless some other condition is present. The urine is generally normal except for a transient albuminuria associated with the more acute febrile stages of the disease.

The diagnosis both of tularemia and of tularemic pneumonia is frequently overlooked. In reviewing the literature, Kennedy[39] was impressed particularly with the lack of clinical recognition of the pulmonic form of tularemia.

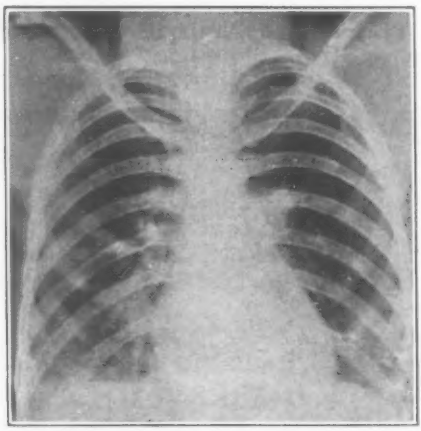

FIG. 2.—(Case 21.) The chest on Jan. 29, 1943. Numerous, discrete infiltrations throughout the right lung field typical of bronchopneumonia.

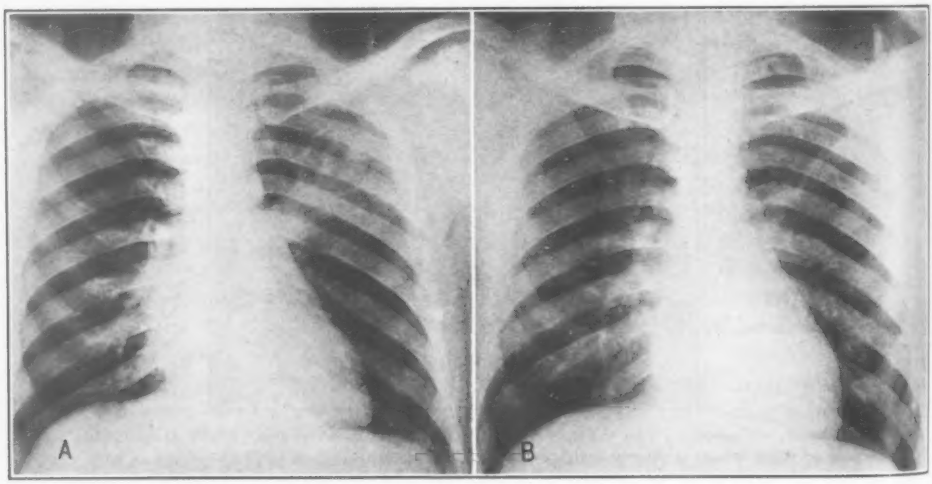

FIG. 3.—(Case 19.) *A*, The chest on Feb. 1, 1940, reveals an infiltration extending upward and outward from the left hilum which could be readily confused with pulmonary tuberculosis. *B*, Twenty days later, clearing of the previous infiltration.

Course. There is little question that tularemic pneumonia may be mild and transient in character, and frequently unrecognized except for roentgenographic evidence. In other cases, however, the pulmonic involvement is a manifestation of a widespread systemic infec-

tion and may contribute largely to the patient's death. As mentioned previously, pneumonia is found in the majority of cases at autopsy and, like tularemic peritonitis or pericarditis, its presence bears grave significance, especially if the involvement is bilateral. Of the 268 cases of tularemic pneumonia that we have collected from the literature (including 15 cases of our own), 161 cases recovered, resulting in a mortality rate of 39.9%.

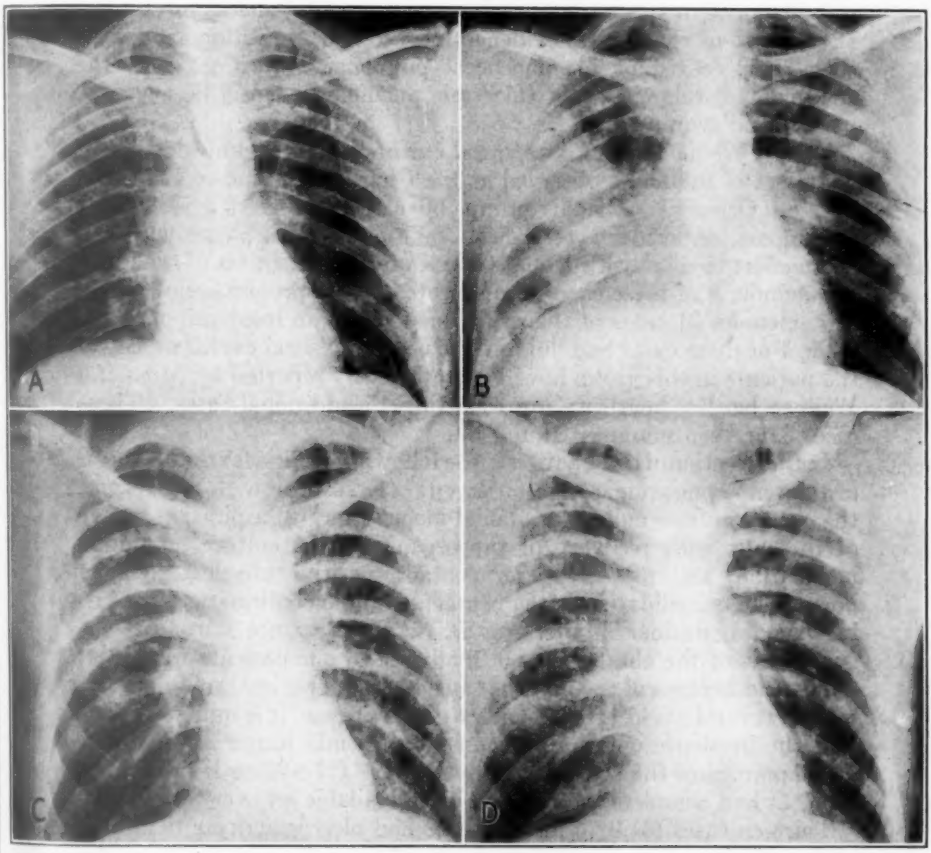

FIG. 4.—(Case 7.) The chest. *A*, On Jan. 28, 1944, slight enlargement of the hilar shadows and several small areas of bronchopneumonia in the right lung base are noted. *B*, Bilateral pneumonic involvement is clearly evident 15 days later. *C*, On May 24, numerous smaller areas of infiltration remain. *D*, On August 8, the lungs have cleared considerably, although some residual linear strands suggesting fibrosis remain.

The duration of the pneumonia is variable. It may last from a few days to several weeks. When the pulmonary involvement persists longer than 3 weeks, some complication, such as a lung abscess, secondary infection, or fibrosis, should be suspected.

Treatment. The specific treatment of tularemic pneumonia is a question that has not yet been finally answered. Specific immune

serum, according to Foshay,[23] is of aid in reducing the severity and duration of the symptoms, especially when given early in the disease, and may possibly be of assistance in treating tularemic pneumonia. Reports of several cases[35,54,66] treated with the sulfonamides have recently been published. Ransmeier,[52] however, found sodium sulfadiazine ineffective against *B. tularense* as demonstrated experimentally *in vivo*. Although little data concerning the effectiveness of penicillin against *B. tularense* have been collected thus far, it would appear that it is no more effective than other therapeutic agents generally available. It seems to us that unless evidences of secondary infection are found, such as a coëxistent pneumococcal pulmonary infection, that the treatment of tularemia and tularemic pneumonia is still largely supportive and symptomatic.

Data. We have recently reported our findings in a clinical study of 225 cases of tularemia observed at the Charity Hospital of Louisiana at New Orleans.[50] Of this group, 30 cases presented evidences of pneumonia, an incidence of 13.3%, while 7 cases had pleural effusion. In an effort to establish adequate criteria for the diagnosis of tularemic pneumonia, 9 of these cases were rejected. The present series, therefore, includes 21 cases of tularemic pneumonia, an incidence of 9.3%, while 4 of these cases had fluid in one or both pleural cavities. Six of the patients in this group have been previously reported by Moss and Weilbaecher,[47,66] hence we are reporting 15 additional cases. These cases have been summarized in Table 1.

In the selection of these patients, the following criteria for the diagnosis of tularemic pneumonia were observed: (1) autopsy with recovery of the organism from culture or animal inoculation; (2) aspiration biopsy of the lung with recovery of the organism from culture or animal inoculation; and (3) history of contact, positive physical signs of pneumonic consolidation with roentgenographic confirmation and rising blood agglutination titers for *B. tularense*. Since routine roentgenograms of the chest were not made on all our patients with tularemia, and because of the fact that an occasional patient would present himself several weeks after the onset of the disease, it is quite probable that the incidence of pleuropulmonary tularemia in our series would have approached the figures given by Foshay[23] (17.8%) or Kavanaugh[37] (12.7%) had complete information been available on every patient.

Thirteen cases (61.9%) in this series had ulceroglandular tularemia with definite pulmonary involvement. However, only 7.1% of the total number of 181 cases of ulceroglandular tularemia observed at Charity Hospital developed pleuropulmonary tularemia. Eight cases (38.1%) were of the typhoidal type of tularemia and, in turn, 57% of the 14 cases of typhoidal tularemia at Charity Hospital had pulmonic involvement.

Twelve of these 21 patients gave a definite history of contact with rabbits. In 1 other patient, a 59 year old colored male farmer, the only history of exposure was that of a scratch inflicted by a rat. Of the remaining 8 patients from whom no history of contact was obtained, 7 were moribund on admission and expired without giving a satisfactory history.

TABLE 1.—CLINICAL DATA CONCERNING 21 CASES OF TULAREMIC PNEUMONIA

TABLE 1.—CLINICAL DATA CONCERNING 21 CASES OF TULAREMIC PNEUMONIA

Case No.	Age	Color	Sex	Type of tularemia	Contact	Duration of symptoms before pneumonia (days)	Type of pneumonia	Associated findings	Diagnosis	Duration of pneumonia (days)	Remarks
1	59	C	M	U.G.	Rat	8	Broncho	Lues, cirrhosis	Rising agglut. titers	32	Recovered
2	33	W	M	U.G.	Rabbit	13	Broncho	....	Rising agglut. titers	15	Recovered
3	40	C	M	U.G.	Rabbits	Few hrs.	Broncho (bilat.)	Chr. cholecystitis	Animal inoc. (postm.)	1–	Autopsy
4	40	C	F	U.G.	Rabbits	12	Lobar	....	Rising agglut. titers	2	Death—no autopsy
5	58	W	F	U.G.	...	14	Broncho (bilat.)	Diabetes mellitus, nephrosclerosis	Rising agglut. titers, animal inoc. (postm.)	9	Autopsy; complication: uncontrolled diabetes mellitus
6	43	W	F	T.	Rabbit	14	Lobular	....	Rising agglut. titers	33	Recovered
7	59	C	M	T.	...	10	Broncho (bilat.)	....	Rising agglut. titers, lung aspir., biopsy; animal inoc.	22	Recovered
8	33	C	M	U.G.	Rabbit	21	Broncho	Lues	Rising agglut. titers	38	Recovered
9	32	C	F	U.G.	Rabbit	13	Broncho	Rt. pleural effusion	Rising agglut. titers	48	Recovered
10	33	W	M	U.G.	Rabbit	18	Broncho (bilat.)	....	Rising agglut. titers	24	Recovered
11	53	C	F	U.G.	...	10	Broncho (bilat.)	Thrombosis left femoral vein	Lung aspir., biopsy; animal inoc.	12	Death—no autopsy
12	34	C	M	T.	...	10	Broncho (bilat.)	Meningitis	Animal inoc. (postm.)	5	Autopsy
13*	22	C	M	T.	...	6	Broncho	Lung abscess	Animal inoc. (postm.)	4	Autopsy
14*	26	C	M	T.	Rabbit	8	Broncho (bilat.)	Rt. pleural effusion, Type VIII pneumococci in sputum	Animal inoc. (postm.)	2	Autopsy
15*	21	C	F	T.	...	..	Mult. abscesses	Malig. neutropenia			
16	50	C	F	T.	...	12	Broncho	Lues, cholelithiasis	Animal inoc. (postm.)	2	Autopsy
17	39	C	M	U.G.	Rabbit	9	Broncho	Benign prostatic hypertrophy; pleural effusion	Animal inoc. (postm.)	5	Autopsy
18*	30	W	M	U.G.	Rabbit	12	Broncho (bilat.)	....	Lung aspiration, biopsy; animal inoc.	3	Autopsy
19*	30	C	M	U.G.	Rabbit	9	Lobular	....	Rising agglut. titers	? (deserted)	Probably recovered
20*	26	C	M	T.	...	9	Broncho (bilat.)	Lues; Type X pneumococci in sputum	Rising agglut. titers, lung aspir., biopsy; animal inoc.	29	Recovered
21	27	C	F	U.G.	Rabbit	12	Broncho (bilat.)	Pl. effusion (bilat.)	Rising agglut. titers; animal inoc. (postm.)	19	Autopsy
									Animal inoc. (postm.)	9	Autopsy

* Denotes cases previously reported by other investigators.[47,66]

The occurrence of tularemic pneumonia in 13 males as compared to 8 females is proportional to the sex incidence for our entire group of tularemic patients (134 males and 91 females). The incidence of pulmonary involvement in 16 colored patients as compared to 5 white patients may be significant, however, inasmuch as 132 of the 225 tularemic patients studied were white as compared to 93 colored patients.

The occupational history revealed that two-thirds of this group consisted of housewives, farmers, cooks, butchers and peddlers and, as stated, was related to exposure to rabbits in all but 1 instance. In the remainder the occupation was such as to appear unrelated to the development of the disease.

The incubation period varied from 24 hours to 10 days in 12 cases in which an adequate history could be obtained. The average incubation period for this group was 4.5 days. It is of interest to compare this with Kavanaugh's observation[37] of 4.5 days in 123 cases of tularemia and Foshay's determination[23] of 3.3 days as the average incubation period of 600 collected cases of tularemia.

The duration of symptoms before the diagnosis of pneumonia was established varied from a few hours to 21 days, with an average of 11 days. The known duration of tularemic pneumonia in 12 cases before death varied from 22 hours in 1 instance to 19 days in another, while the average duration for this group was slightly more than 6 days. In 8 surviving cases the known duration of pulmonary involvement varied from 15 days in 1 case to a maximum of 48 days in another, with, however, an average of 30 days. One patient deserted the hospital before complete recovery.

The diagnosis of tularemic pneumonia was definitely established in 8 patients that eventually recovered by demonstrating rising blood agglutination titers for *B. tularense*. Three patients were diagnosed in a similar manner before death. Aspiration biopsy of the lungs with guinea pig inoculation confirmed the diagnosis in 2 patients that subsequently recovered from the disease and 1 that succumbed. Eight of the group had no definite diagnosis before necropsy was performed; in 4 of these patients, however, tularemia was suspected because of the presence of primary lesions and lymphadenopathy or a definite history of handling rabbits.

Nine of our 21 patients recovered from the disease while 12 died, a mortality rate of 57% in 21 cases of tularemic pneumonia. Autopsies were secured on 10 patients. Curiously, 6 of 8 females with tularemic pneumonia expired, whereas only 6 of 13 males in this series died. The only white patient (a female) that died probably expired as a result of uncontrolled diabetes mellitus, and the death of 1 colored female may possibly be attributed to a malignant neutropenia following sulfonamide therapy.[47]

In addition to the sex factor, a racial predisposition was noted. Thus, 11 of the 12 deaths were in Negroes, a mortality rate of 69% of the 16 colored patients in our group.

Summary. 1. Up to September 1944, 253 cases of tularemic pneumonia were collected from the American literature and we have reported 15 additional cases herein.

2. Criteria for the diagnosis of tularemic pneumonia have been outlined.

3. Of 225 cases of tularemia observed at the Charity Hospital of Louisiana at New Orleans, 21 cases (9.33%) had accompanying tularemic pneumonia.

4. The incidence of tularemic pneumonia is distinctly greater in the typhoidal forms than in the ulceroglandular types of tularemia. Thus, only 13 (7.1%) of 181 cases of ulceroglandular tularemia developed pleuropulmonary involvement, whereas 8 cases (57%) of 14 instances of typhoidal tularemia developed clinical tularemic pneumonia.

5. Of our 21 patients with tularemic pneumonia, 12 (57%) expired.

6. Although our incidence of tularemia in colored patients as compared to white patients is proportional to the total admissions of white and colored patients at Charity Hospital for the same period of time, it would seem from our findings that Negroes are particularly lacking in resistance once they have developed the pulmonic forms of the disease. This is evidenced by the fact that 16 of our 21 cases of tularemic pneumonia were colored and that 11 of these 16 patients expired. Whether this racial susceptibility is due to lack of immunity, or inability to develop immune bodies, or whether environmental, dietary and other factors associated with a lower standard of living are responsible is a question that we must leave unanswered. Only 1 white patient expired, and this may be attributed in part to an uncontrolled diabetes mellitus.

7. Curiously, 6 of 8 women with tularemic pneumonia died, as compared to 6 of 13 men. Analysis of the charts suggests that the sex predisposition may have been coincidental.

8. In patients who recovered, the average duration of the pneumonia was 30 days, attesting, therefore, to the marked morbidity as well as mortality of this disease.

9. No specific therapy in our hands has been beneficial. The patient should be supported until the disease has run its course.

10. Every patient with tularemia should be observed carefully both clinically and roentgenographically for the development of pleuropulmonary tularemia. Such patients should, of course, be isolated.

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OSTEOMYELITIS CAUSED BY GRANULOMA INGUINALE

REPORT OF A CASE WITH CULTIVATION OF THE DONOVAN BODY IN THE YOLK SACK OF THE DEVELOPING CHICK EMBRYO

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ALTHOUGH extragenital lesions of granuloma inguinale are not uncommon (lip, mouth, neck, etc.), visceral manifestations of this condition have been reported in but few instances.[6] Skeletal involvement by granuloma inguinale has been noted in only 9 cases.[4,7–13] Since bone lesions are unusual, this case of osteomyelitis of the tibia is reported. Donovan bodies were found in histologic section of biopsies from this case and were cultivated in the yolk sac of developing chick embryos by the method described by Anderson and co-workers.[1–3]

Extragenital lesions of granuloma inguinale are generally believed to be the result of contact infection. Occasionally, however, multiple extragenital lesions are found and their widespread distribution has suggested a hematogenous dissemination.[11] Both the older references of widespread visceral involvement of granuloma inguinale and the more recently reported cases of osteomyelitis complicating genital lesions seem to support this idea of a systemic disease. In many of these cases bone lesions were found in the extremities, thorax, and skull but there were no skin ulcerations. In these patients the spread of the disease by the blood stream must be admitted. That the disease may be systemic is suggested by the following case in which a primary extragenital lesion appeared several weeks before the genital ulcer.

Cultivation of Donovan bodies on bacteriologic media has been unsuccessful[5] and diagnosis depended upon the finding of the organism in spreads or histologic sections. However, 2 new methods of isolating the Donovan body have been reported: one by continuous tissue culture,[9] and the other by the use of the yolk sac of the chick embryo, as described by Anderson.[1] The latter method was successfully employed in this case.

Case Report. C. S., a 43 year old colored male, was admitted to the Orthopedic Service on September 19, 1944, complaining of a sore on his leg. About 6 months before admission he struck his left shin and sustained a bruise which persisted. Three months prior to admission he again injured the bruised area and an ulcer formed. This ulcer gradually increased in size, without local pain or tenderness. One month after the onset of ulceration the patient noticed that the left knee was becoming stiff, although there was no pain on motion. During the month prior to admission the left leg was occasionally painful.

Three weeks before admission the patient first noticed a penile lesion. This

consisted of a small erosion of the dorsum of the shaft of the penis adjacent to the corona. This ulcer gradually spread to involve the circumference of the penis. There was no local pain or tenderness.

The ulceration of the left leg did not confine the patient to bed but he had to walk with a crutch. His appetite remained good, but his weight dropped from 130 to 86 pounds. There were no other systemic symptoms.

The patient gave a history of urethral discharge 20 years ago. This was complicated by a left inguinal bubo which ruptured spontaneously, drained for a short time, and then healed. About 18 years ago he had a lesion on the frenulum of the penis which healed without treatment. He had never had a serologic test or treatment for syphilis.

FIG. 1.—The lesion of granuloma inguinale proximal to the corona of the penis.

The patient denied extramarital sexual contacts during the past year. He stated that his wife had no visible genital lesions.

Despite repeated questioning, the patient insisted that the ulcer on the leg had been present for a long time before the penile lesion appeared.

Physical examination revealed an emaciated, middle-aged colored male whose appearance suggested considerable recent weight loss. The mucous membranes and palms exhibited moderate pallor. His temperature was 98.8° F. on admission, and the pulse and respiration were normal. The blood pressure was 100/80. The skin was loose and lacked normal elasticity. The eyes, ears and nose and throat showed no abnormality. The neck, heart, lungs and abdomen were also normal. There was a scar with slight keloid formation in the left inguinal region.

The penis was circumcised and showed a non-tender, band-shaped ulcer encircling the organ just proximal to the corona. The ulcer measured from 1 to 2 cm. in width. The lesion consisted of red, velvety, friable granulation tissue with sharply demarcated, slightly elevated edges (Fig. 1).

FIG. 2.—The large granulomatous lesion of the left leg. Note the deep ulceration near the upper edge of the lesion which extended into the marrow cavity of the tibia.

The left upper shin showed a large, tender, elevated granulomatous lesion, measuring about 7 x 15 cm. The granulations were exuberant and friable. In the upper portion of the lesion there was a deep, funnel-shaped ulcer about 3.5 cm. in diameter which extended into the medullary cavity of the tibia (Fig. 2).

In the right inguinal region several small, discrete, non-tender lymph nodes were felt; none was noted in the left groin.

The laboratory findings were: R.B.C. count, 4,050,000, with 9.6 gm. of hemoglobin; W.B.C. count, 6200, with a normal differential; urine negative; blood Kahn negative; sedimentation rate 125 mm. in 1 hour. There was no evidence of sickling of the erythrocytes. The blood calcium was 12 mg. per 100 cc.; blood phosphorus, 4 mg. per 100 cc.; serum alkaline phosphatase, 4.6 Bodansky units; total serum protein, 7.7. gm. per 100 cc. Spinal fluid studies revealed nothing abnormal. Ducrey and tuberculin skin tests were positive. The Frei test was negative, but the complement-fixation test for lymphogranuloma venereum was positive to a titer of 1:80.

Roentgenograms of the left leg showed a large bone defect in the proximal tibia at the level of the tubercle. This defect measured about 4 cm. in diameter and extended from the anterior surface of the tibia to its posterolateral aspect,

resulting in dissolution of the cortex. This bone cavity was surrounded by moderate sclerosis. There was irregular periosteal thickening along the medial, lateral, and posterior aspects of the proximal tibia. The width of the knee joint was slightly reduced and the distal femur and tibial condyles showed moderate osteoporosis. The articular surfaces of the tibia and femur were intact. There was no evidence of bony ankylosis. The roentgenologist stated that the findings were consistent with a chronic infection (Fig. 3).

FIG. 3.—Roentgen ray of left tibia, lateral and antero-posterior view. Note the large defect in the tibia with some sclerosis of the surrounding bone and irregular periosteal thickening.

Roentgenograms of other bones were negative except for a cystlike area of rarefaction, measuring 1 x 1.5 cm. in the anterior portion of the 7th rib on the left side. The area of rarefaction was surrounded by a zone of sclerosis and there was no periosteal reaction.

The preliminary clinical impression was that of a tumor of the left tibia. Biopsies from the granulation tissue of the leg and later from the penis showed granuloma inguinale. Two attempts to isolate Donovan bodies from the penile lesion by means of the yolk sac method were unsuccessful because of bacterial contamination. After local applications of a solution of tyrothricin and of sulfanilamide powder in an attempt to eliminate the secondary infection, an osteotomy of the left tibia was done. Biopsies from surface granulation tissue, bone and bone marrow showed granuloma inguinale on histologic section. Donovan bodies were isolated in pure culture by inoculation into yolk sacs of a portion of this material.

Biopsy of the rib lesion was done on the 23rd hospital day, but the specimen did not show granuloma inguinale either by histologic study or yolk sac inoculation.

Treatment consisted of the local application of sulfanilamide powder and tyrothricin to the leg and penile lesions. The tibial defect was packed with iodoform gauze, and the packing changed at frequent intervals. Sulfadiazine was administered orally. Fuadin was given intramuscularly at weekly intervals.

On the 29th hospital day a split-thickness skin graft was applied to the lesion of the left leg. Approximately 90% of the grafted skin survived.

The patient remained in the hospital for 48 days. During the entire period

his temperature never rose above 99° F. He was dismissed 20 days after the skin graft was applied and is now being followed in the out-patient clinic.

The leg lesion is now completely epithelialized except in the area immediately overlying the bone defect. This area is slowly filling in with granulation tissue. The penile lesion shows some healing. Treatment with fuadin is being continued.

Report of Biopsy Material. The various fragments of tissue obtained by biopsy were of reddish-tan color and of meaty consistency. Fragments of bone were attached to the specimens from the tibia and its marrow.

All tissues were fixed immediately in Zenker's fluid with 5% glacial acetic acid and in a 10% solution of formalin U.S.P. Eleven sections stained with phloxine-methylene blue were examined.

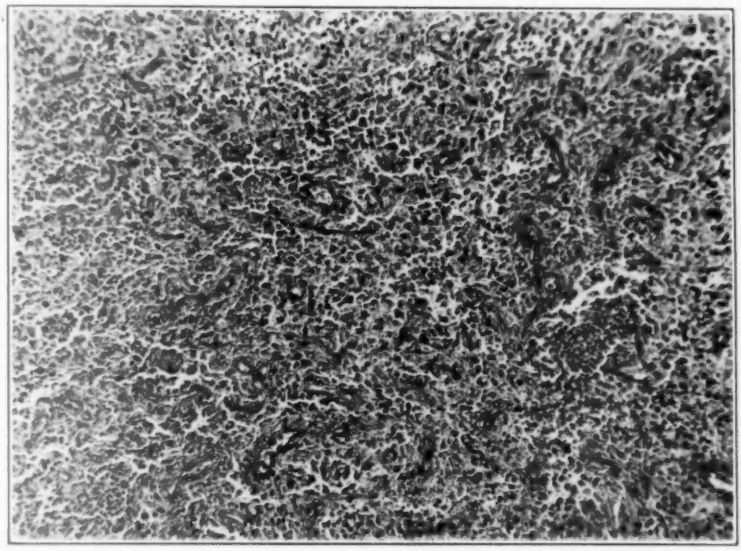

FIG. 4.—The granulation tissue with microabscesses from the lesion of the leg. This general pattern is quite suggestive of granuloma inguinale. Phloxine-methylene blue X 105.

The histologic picture was the same in the various tissues. It consisted of a richly vascularized granulation tissue with marked inflammatory cell infiltration (Fig. 4). There were numerous plasma cells and lymphocytes, but there was a predominance of large mononuclear cells and neutrophilic polymorphonuclear leukocytes. The polymorphonuclear leukocytes were scattered throughout the tissue or formed small and medium sized microabscesses. The large mononuclear cells were dispersed throughout the tissue and showed a finely reticulated or vacuolated cytoplasm. Phagocytosis of polymorphonuclear leukocytes and other cellular débris by these cells was common.

A large number of the mononuclear cells contained typical Donovan bodies. Sometimes as many as 8 cells laden with Donovan bodies were encountered in a single oil immersion field. These infested cells were most numerous at the periphery of the microabscesses but were also found elsewhere. All stages of infestation were noted in these cells. Sometimes only small groups of Donovan bodies occupied a part of the cytoplasm, while in other instances the entire cell body was invaded. In some cells the cytoplasm appeared cystic; in others, rupture of the cell body had occurred.

Some proliferation of fibroblasts and deposition of collagen was encountered in a few areas, but this process had not progressed significantly.

The sections of the bone and bone marrow showed spicules of degenerating and necrotic bone without appreciable new bone formation.

The epidermis at the edges of the lesion was necrotic and infiltrated by polymorphonuclear leukocytes. There was no regeneration.

Numerous mononuclear cells laden with Donovan bodies were seen on the ulcerated surface of the lesion together with occasional cocci. No microorganisms were identified elsewhere in the sections.

Cultivation of Donovan Bodies. The surface granulation tissue, bone marrow, and adjacent tissue were all found to contain Donovan bodies on impression smears stained by Wright's method. The organisms were grown from the surface granulation tissue in the yolk sac of chick embryos by the method described by Anderson and co-workers.[1,2,3] Cultures on blood agar and in thioglycollate revealed no bacteria in the inoculum or in the material harvested from eggs. From bone marrow and adjacent tissue, however, Donovan bodies were not isolated because the inoculum contained a slowly growing alpha streptococcus which killed the chick embryos.

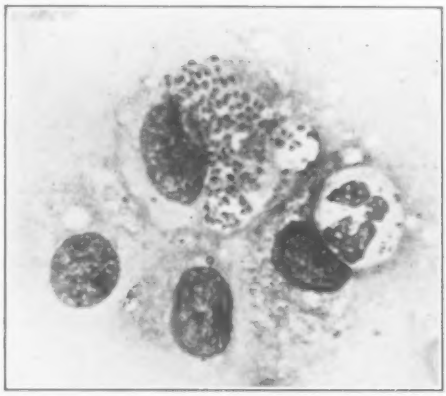

FIG. 5.—Impression smear of granulation tissue adjacent to the tibia. A large mononuclear cell with numerous typical Donovan bodies. The cytoplasm of this cell is characteristically vacuolated. Wright stain × 1000.

The details of the cultivation of the Donovan bodies are as follows: Granulation tissue from beneath the surface of the lesion was triturated in a mortar and made into a 10% suspension with saline solution. Following a low-speed centrifugation, the supernatant material was injected in 0.6 cc. amounts into the yolk sacs of 15 6-day-old embryos. The eggs were then reincubated at 37° C. Three embryos were dead the following day and were discarded. Two died on the 2nd day and were also discarded because impression smears of their yolk sacs revealed no microörganisms. Smears of yolk and yolk sacs harvested from living embryos on the 2nd, 3rd and 4th days showed progressively increasing numbers of Donovan bodies. The remaining eggs were harvested on the 7th and 11th days and were found to contain a few clusters of intracellular bodies. Second passage of the agent was initiated with material taken on the 4th day. A yolk sac was mixed with yolk from the same egg, shaken with glass beads on a shaking machine, and inoculated in 1 cc. amounts into 11 6-day-old embryonated eggs. This 2nd passage produced a moderate growth of Donovan bodies by the 3rd day and a rich yield on the 4th day. Successive passages of the agent shortened the incubation period to 3 days, so that harvests made at this time contained a large number of bodies. Eight serial passages were made and in each one the Donovan bodies presented the same

morphology. Bacteriologic cultures on blood agar, in thioglycollate, and occasionally in tryptose-phosphate broth containing agar, yielded no growth from yolk or membranes of each passage.

The morphology of Donovan bodies was observed by impression smears of human and yolk sac material, stained by Wright's method. With spreads of infected yolk, flooding the slide with ethyl ether before staining removed much of the yolk and consequently facilitated the search for Donovan bodies. The morphology of the organisms was not changed by this procedure. Touch smears of human granulation tissue revealed the bodies to be of variable morphology. They consisted chiefly of forms resembling closed "safety pins," diplococcal forms or encysted clusters of single bodies, with a few encapsulated organisms present. The majority of them occurred intracellularly (Fig. 5). When cultivated in embryonated eggs, the Donovan bodies were shown to have a morphology similar to that seen in smears of human material. "Safety pin" and shorter, bipolar forms predominated, although curved rods and encapsulated types were often observed in the same preparation (Fig. 6).

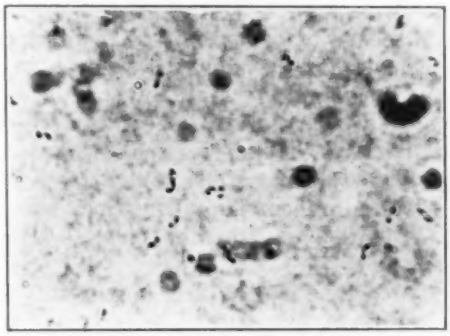

FIG. 6.—Donovan bodies in a spread of yolk infected with the fourth passage of the agent cultivated in embryonated eggs. Wright stain × 1000.

Discussion. The occurrence of osteomyelitis caused by granuloma inguinale is uncommon. We have found only 4 cases in the literature in which the diagnosis was proven by histologic examination.[9,11] The other cases[10,12,13] must be regarded as less authenticated, for the diagnosis of granuloma inguinale was based entirely on the isolation of bacteria thought to be the etiologic agent. These latter case reports describe widespread visceral involvement with multiple granulomatous abscesses of the bone, liver, lungs, spleen and intestine.[6–8,12,13] There are recent reports, however, of arthritic manifestations with extensive lesions in the joints of the hands and feet.[9]

In some of the reported cases there was an extension of the skin granuloma into the underlying bone, while in others the skin ulceration was secondary to the breakdown of the bone lesion. In our case, we could not be certain whether the bone or skin was the primary site of the extragenital lesion, for both tissues were involved when the patient was first seen.

In the majority of cases reported a moderate amount of local pain and tenderness was present over the bone lesions. There were rarely any signs of an acute inflammatory process. Generally, systemic symptoms of malaise, weight loss, low grade fever, and anemia were

noted. The patients usually pursued a chronic course of remissions and relapses. Among the proven cases only 1 death occurred.[9]

Occasionally an elevation of the serum globulin and of the alkaline phosphatase level was noted. The roentgenograms usually revealed a lytic bone lesion with little evidence of new bone formation. This was also found in our patient, in which there appeared only a slight sclerosis about the area of destruction. In some instances the bone lesions responded to antimony therapy,[11] while in 1 case successive amputations were necessary before the infection could be controlled.[9]

The diagnosis of bone involvement is usually made by finding Donovan bodies in impression smears or histologic sections. The organism was reported to be isolated in continuous tissue culture from one of the cases reported by Lyford *et al.*[9] In our patient the organism was cultivated in the yolk and yolk sac of chick embryos from the granulation tissue of the leg. In our work the technique described by Anderson provided a useful means of demonstrating this organism. Anderson and co-workers[2,3] have recently published reports which conclusively indicate that the Donovan body is the etiologic agent of granuloma inguinale. Donovan bodies were not isolated from the tibia because of bacterial contamination of the biopsied specimen, although they were found in smears and histologic sections of the bone. The cystic lesion of the rib was suspected of being granuloma inguinale, but showed no evidence of this condition in either histologic sections, or yolk sac cultures.

Our patient insisted that the leg ulcer appeared 9 weeks before the onset of the genital lesion. We cannot be certain of the pathogenesis or of the sequence of events in this patient. The leg ulcer might represent a primary extragenital lesion with secondary contact infection of the penis. It is also possible that the penile lesion was present at the same time as the leg ulcer, but was too small to be noticed by the patient. In either event the patient's and the physician's attention was directed to the leg lesion. The correct diagnosis was not suspected clinically, but was made by biopsy of the leg ulcer.

The possibility of extragenital granuloma inguinale should be considered in cases of chronic skin ulceration and even in non-healing osteomyelitis, regardless of location. Just as in syphilitic infection, the absence of a genital lesion need not exclude the possibility of systemic granuloma inguinale. It is striking that all proven cases of skeletal granuloma inguinale have been reported within the past year. Once it is realized that systemic manifestations of this disease occur, other instances of disseminated granuloma inguinale will be noted.

Summary. 1. A case of osteomyelitis of the tibia caused by granuloma inguinale is reported.

2. Donovan bodies from this case were cultivated in the yolk and yolk sac of the chick embryo according to the method described by Anderson.

3. A review of the literature reveals that bone involvement by granuloma inguinale is rare, but when found may be a manifestation of the systemic nature of this disease.

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HEMOCHROMATOSIS ASSOCIATED WITH PRIMARY ADENOCARCINOMA OF THE LIVER

A Case Illustrating Diagnostic Features

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It has been noted in several pertinent papers of the past 13 years that primary carcinoma of the liver complicates some 7% of cases of hemochromatosis. Yet, because of the rarity of hemochromatosis, the total number of cases occurring with associated primary hepatic carcinoma is small. Berk and Lieber,[1] in 1941, by adding 3 cases of their own to a previously reported 29, brought the total number of acceptable cases to 32. Since then, and up until the end of September 1943, Willis[4] has added 3 and Saward[3] 1 case. With the case herewith reported, the recorded number of cases of hemochromatosis with primary carcinoma of the liver mounts to 37.

Correct preoperative or antemortem diagnosis of these diseases in association has not been made, to the best of our knowledge. Careful consideration of the symptoms produced directly by the malignancy and of the variations in the expected course of hemochromatosis, which appear following the development of malignancy, should, however, lead to correct diagnosis. The diagnostic features have been set forth

and thoroughly reviewed in a recent communication.[1] Briefly, the symptoms which should lead to suspicion of hepatoma complicating hemochromatosis are: rapid progression of symptoms; abdominal pain as an outstanding complaint; jaundice; ascites, particularly sanguinous and not occurring as a terminal phenomenon; a massive liver, hard in consistency and nodular, or with disproportionate enlargement of the right lobe; amelioration of severity of the diabetes with undue liability to hypoglycemia; fever; anemia; leukocytosis; loss of weight; and evidence of metastatic involvement in lungs or other organs.

Of these symptoms some, notably pain, jaundice, ascites, and loss of weight (due to uncontrolled diabetes), are seen in uncomplicated hemochromatosis, but so rarely as to make their appearance strongly suspicious of the presence of an added neoplastic factor.

The case reported below presents many of these diagnostic features.

Case Report. J. M., a Filipino, aged 48, a ship's steward, was admitted to the hospital on Jan. 29, 1944. Family history was unknown to him and previous diseases were denied, with the exception of gonorrhea and syphilis about 1933, both apparently adequately treated.

Patient stated that he had been in good health up until 1 month before admission, when he noted the onset of mild aching pain in the epigastrium, constant and not accentuated or relieved by food, and without radiation. One week before admission, yellow-brown staining of the skin, scleræ and urine appeared, but the color of the stool was not noticed. Patient weighed 135 pounds 2 years ago, and on admission weighed 113 pounds, the greatest loss of weight having occurred in the month prior to admission. Generally, he felt weak and complained of some dizziness when lifting. History was otherwise negative by systems; tobacco and alcohol were used in moderation.

Physical examination revealed patient to be a thin, slightly built Filipino male, appearing about his stated chronologic age, deeply jaundiced, with scattered excoriations and 2 spider telangiectases on chest. The pupils were pin-point and irregular and did not react to light. Fundi were normal. Head and neck were otherwise negative. Blood pressure 100/68. There was a soft systolic blow heard loudest at the apex but no other abnormal heart findings. The lungs were clear throughout. The liver border was thought to be palpable some 2 to 4 cm. below the costal margin and not tender, but no other pathologic findings were noted. Rectal examination was negative. The extremities presented no significant findings and, with the exception of depression of the deep reflexes of the legs, neurologic examination was normal.

During the first 2 weeks of observation, the stools were observed to be light yellowish and on several occasions were negative for parasites and ova. Except for marked bile staining and a 4+ sugar reaction, repeated urinalyses were negative. Gastric analysis showed a maximum free acid of 40 and combined of 70 degrees. The blood Wassermann test was negative. The erythrocytes numbered 3,800,000 and the leukocytes 11,050 (neutrophils 65%, lymphocytes 33%, monocytes 2%, and eosinophils 2%). The hemoglobin was 70%. The sedimentation rate was 27, icterus index 159.5, and fasting blood sugar 287.8 mg. Hippuric acid liver function test yielded 0.3 gm. The bleeding time was 1 minute and the coagulation time (Lee and White) 5 minutes. Roentgen ray of the lungs was reported as showing a healed gland in the right hilar region and a healed tubercle at the right base. Gastro-intestinal series was essentially negative with the exception of slight "pattern variation" in the distribution of the barium in the colon. A flat plate of the abdomen was suggestive of an enlarged spleen but not of enlarged liver. It was found impossible to fill the gall bladder. During this period and subsequently, there was no abdominal pain. Low grade fever, not exceeding 37.6° C. was noted on several occasions.

During the period from Feb. 12, 1944, to the middle of March, 1944, the patient apparently did well. A diet containing C 230, P 85, F 45 was taken daily, and at the beginning of the period 30 units of protamine zinc insulin were given each day. On February 15, this was increased to 35 units, which dose was maintained until February 21, when 32 units were given. Successive reductions were 27 units on February 25, and 20 units on February 28. On this regimen, small amounts of sugar appeared in the urine at first, but all later specimens showed either no sugar or traces too small to be quantitatively estimated. The patient felt stronger and gained a few pounds in weight. The stool was bile-stained for the most part, but occasionally clay-colored stools were noted. The icterus index was 252 on February 18, 240 on February 23, 225 on March 1, 196 on March 10, and 192 on March 14, 1944.

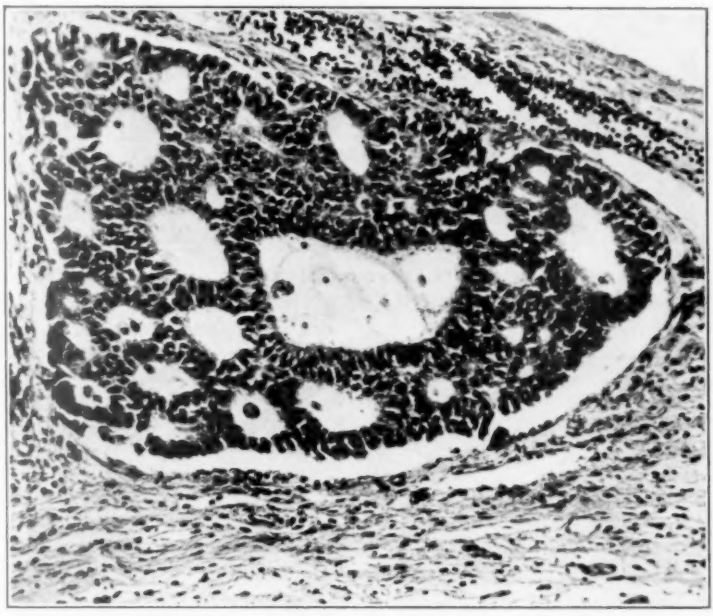

FIG. 1.—Liver showing adenocarcinoma and cirrhotic stroma. Van Giesen-Weigert iron chloride. × 175.

From the middle of March to March 27, a small amount of edema of the legs was noted and toward the end of the period frank ascites developed. A feeling of well-being continued, however, and patient's general condition was considered fair. On one or two occasions, there was some bleeding from the gums which stopped after the administration of vitamin K for several days. The icterus index, however, again started climbing and patient's stools were noted to be clay-colored. On March 17, the icterus index was 210 and on March 25, 240. Serum protein on the latter date was 5.7 gm. On March 27, total blood cholesterol was 170, icterus index 300, and Van den Bergh immediate direct positive. The urine continued sugar-free and there was gain in weight of several additional pounds attributed to the development of ascites. Low grade fever not exceeding 37.5° C. was noted at intervals of several days.

On March 27, 1944, exploratory laparotomy was performed. On opening the abdomen, approximately 1 quart of ascitic fluid, brownish in color, was aspirated. The liver was uniformly studded with small bluish-green nodules

and generally dark. The spleen was moderately enlarged. The pancreas, common duct, stomach, and duodenum were regarded as normal. The gall

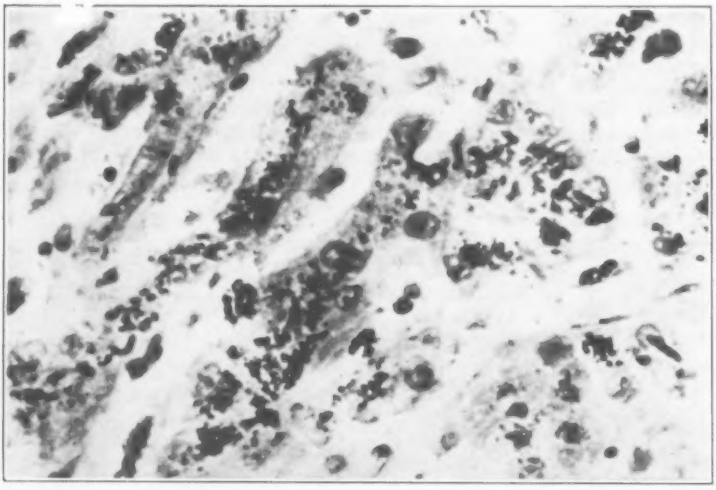

FIG. 2.—Liver showing Prussian blue reaction for hemosiderin. Note clusters of granules within the cells of the hepatic cords. × 700.

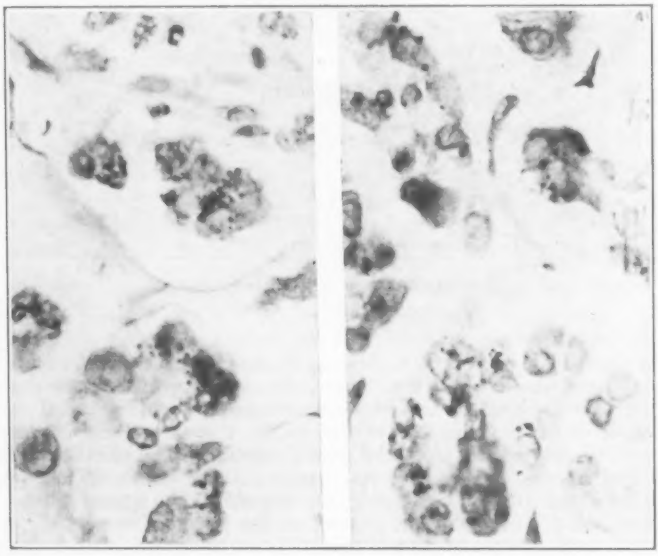

FIG. 3.—Pancreas showing Prussian blue reaction for hemosiderin. Note hemosiderin granules within the epithelial cells of acini. × 1000.

bladder was contracted and small. Some lymph nodes were palpable retroperitoneally behind the common duct. A small wedge was taken from the anterior right lobe of the liver for histologic study.

Liver Biopsy. *Gross.* A nodular, bile-stained liver specimen roughly 1.5 cm. in diameter.

Microscopic. There was intense thickening of the periportal stroma accompanied by a dense infiltrate of neutrophils, plasma cells, and lymphocytes. The liver lobules were of various sizes and had lost relationship to the central veins. The hepatic cells were often enlarged, their cytoplasm frequently granular and vacuolated and in many was a large amount of granular brown pigment which, with special staining, was shown to be hemosiderin. In addition to hemosiderin many liver cells and some bile ducts contained masses of greenish-yellow pigment. A little hemosiderin was seen in the stroma.

Diagnosis. Hemochromatosis with associated portal cirrhosis and chronic active hepatitis.

From March 27, 1944, the patient progressively became less interested in life. During this period, although at least 200 gm. of carbohydrate were administered daily, intravenously or orally, no sugar ever appeared in the urine and blood sugar was 114 mg. Insulin intake was gradually reduced. On April 1, the dose was 16 units, on April 7, 10 units, and on April 8, 1944, the last reduction was made to 5 units. Stools during this period were completely clay-colored, the urine darkly bile-stained.

The patient became comatose 2 days before death which occurred April 10, 1944.

Autopsy (Dr. J. D. Gioia). The skin of the forehead and neck was bronze in color and the trunk and extremities a deep greenish-yellow. The body hair was abundant and the distribution normal. There was pitting edema of the lower back and of the ankles and feet.

Abdomen. The peritoneal cavity contained 2500 cc. of serosanguinous fluid. The liver edge was 5 cm. below the costal margin.

Thorax. The left pleural cavity contained 100 cc. of clear fluid similar to that seen in the abdomen.

Heart. Weight 290 gm. Appeared normal.

Aorta. Normal with exception of several atheromatous patches.

Lungs. Right 510 gm., left 760 gm. Each lower lobe was firm and noncrepitant, dark red in color and on section was homogeneous in appearance. The mid-lobe and upper lobe were moderately crepitant. On section profuse foamy golden yellow serous fluid exuded.

Gastro-intestinal Tract. The esophagus, stomach, and intestines appeared normal.

Liver. Weight 1590 gm. It appeared smaller than normal and was very firm. Surface of the left lobe was studded with blue-black nodules which range from 1 mm. to 1 cm. in diameter. The color of the tissue which formed the intervening depressions was greenish-gray. The cut section appeared similar to the external surface. Portal canals and hepatic veins were distended. The left lobe externally appeared the same as the right but sections revealed clusters of conspicuous soft, yellow nodules of from 1 to 5 mm. in diameter. The caudate lobe stood out as if a large egg were distending its capsule. On sectioning numerous discrete nodules of from 0.5 to 2 cm. in diameter were revealed. Inferiorly overlying the vena cava and encircling the hepatic and cystic ducts was a mass about 4 cm. in diameter. On sectioning this mass resembled that seen in the caudate lobe.

Gall Bladder. Of normal size; contained gelatinous inspissated bile.

Spleen. Weight 210 gm. Except for the slight increase in size, appeared normal.

Pancreas. Weight 120 gm. Appeared normal in size and shape; it was of firm consistency and light yellow in color.

Kidneys. Right 200 gm., left 180 gm. Each was bile-stained but otherwise appeared normal. The urinary bladder, prostate, and testis were bile-stained but in other respects seemed normal. Adrenals and thyroid appeared normal. The central nervous system was not examined.

MICROSCOPIC. *Liver.* As observed in the biopsy, there was portal cirrhosis and the same type of hemosiderin pigmentation was present in the liver cells.

There was relatively more hemosiderin in the periphery of the lobules. Some hemosiderin granules were also seen in the bile capillaries and in phagocytic cells of the stroma. Occasionally a lobule of liver cells showed very little pigment. The tumor consisted of cords and acini of large polyhedral cells with leptochromatic nuclei and granular amphophil cytoplasmic zones. The pattern was moderately uniform. Cells in mitosis were seen in small numbers. In some areas, a few tumor lumina contained mucoid material. As it was supported by the liver stroma, the tumor assumed a lobular pattern somewhat like that of the preëxisting liver.

Pancreas. There was a diffuse mild interstitial fibrosis. This stromal fibrosis occasionally involved an islet. There were clusters of hemosiderin pigment granules in the lining cells of many acini.

Spleen. There were widened sinuses and some thickening of the pulp stroma. There was considerable hemosiderin either free or in phagocytic cells.

Kidney. The glomerular capillaries appeared swollen and nearly filled the capsules. The proximal and distal convoluted tubules exhibited swollen and often degenerating epithelial cells. Numerous bile casts were present. An area of suppuration about 0.5 cm. in diameter was seen in a papilla.

Skin. In a section from the leg there were many granules of hemosiderin pigment deposited about the capillaries or glands of the corium. Specimens from the chest and shoulder were without pigment.

Breast, adrenal, testis and thyroid showed no deposition of hemosiderin; unfortunately no specimen of heart was examined. The lung showed emphysema and a terminal pyogenic bronchopneumonia. The gall bladder exhibited chronic active cholecystitis.

A quantitative analysis* for iron yielded 50 mg. in 32 gm. of formalin fixed liver. On this basis it was estimated that the total organ contained 2.484 gm. The average iron content in human liver found by Donath,[2] as result of 260 autopsies, was 258.1 mg. Therefore, this liver contained an estimated 10 times the normal amount of iron.

Discussion. The adenocarcinoma probably arose in the intrahepatic biliary duct system. The ensuing obstructive jaundice was an important factor in bringing about death though the tumor had involved a relatively small part of the liver and had not metastasized. The portal cirrhosis and hemosiderosis of the liver, the early diffuse fibrosis and hemosiderosis of the pancreas and the clinical diabetes appear sufficient evidence to warrant a diagnosis of hemochromatosis even though deposition of hemosiderin in the liver and pancreas was not as heavy as is usually seen in postmortem examinations of people dying of this disease. Had the tumor not caused death by biliary obstruction it is probable that the classical features of hemochromatosis would later have developed.

The iron pigmentation in the specimen of skin removed from the anterior part of the leg cannot definitely be interpreted as a disturbance in iron metabolism as this area is subject to much minor trauma and skin specimens from the shoulders and neck showed no iron. The spleen is so frequently the site of iron pigmentation that the relatively large amount of hemosiderin there is not considered to be of diagnostic value.

Summary. The case of a Filipino male, aged 48, who showed clinical and pathologic features of hemochromatosis complicated by obstruc-

* The analysis for iron was made by Principal Industrial Toxicologist, L. T. Fairhall, Division of Industrial Hygiene, National Institute of Health, Bethesda, Md.

tive jaundice due to adenocarcinoma, is reported. This brings to 37 the recorded number of cases of hemochromatosis associated with primary hepatic carcinoma.

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SURGERY

UNDER THE CHARGE OF
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WOUNDS OF THE HEART

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SURGERY of the heart, while still limited in scope, is today not so unusual a procedure as it was even so short a time as 20 years ago. Consistently successful attempts to ameliorate certain chronic heart disease entities have been reported only in recent years.[10,25] A much longer experience has accumulated with regard to surgical intervention in cases of cardiac trauma, but even in this regard, surgery of the heart has not been practiced for long. A review by Vaughan[44] in 1909 reported 150 cases in which surgery had been performed on traumatic lesions of the heart. Sir Charles Ballance[1] presented a good review of the early concepts regarding this subject.

In 1687, Barbette[2] of Amsterdam stated that wounds of the heart are always mortal and those that penetrate into the left ventricle kill suddenly. Those so wounded seldom live 12 to 20 hours, although occasionally one finds an example to the contrary. Tourby,[41] in 1642, did an autopsy on a man who 4 years previous had had a sword thrust in the chest which caused a wound in the heart near the apex; the evidence of which was a cicatrix that could be easily demonstrated.

In the centuries to follow there is little to note until the eighteenth, when Bonetus,[9] in 1700, and Morgagni,[34] in 1730, established the facts that a sudden filling of the pericardial sac arrested the heart's action and that wounds of the heart were not necessarily immediately fatal. Bonetus[9] relates the case of a young man, age 24, who bravely sustained an attack by 7 others and was at length wounded by a sword thrust. He survived 5 days. The wound was of the left lung and of the right ventricle of the heart.

Morgagni[34] notes two types of heart wounds. In one there was an opening in the pleura as well as the pericardium and the blood escaped freely into the pleural space. Likewise, blood escaped freely externally. In 1 case,

* Now on Active Service in the Armed Forces.

with external bleeding, the patient survived 8 days; in another case the blood was retained in the pericardial sac and the patient died within a few minutes. He points out that the second case did not die from hemorrhage but from pressure on the heart. Thus, as pointed out by Morgagni, a hemorrhage within the pericardial sac, in spite of the small amount of blood lost, may be quickly fatal.

In the early nineteenth century many surgeons regarded operative procedures on the heart as hopeless. Dupuytren[20] advised venesection to be carried out almost to the point of exsanguination as a treatment for wounds of the heart. Guthrie[26a] in 1848 stated that in all of London with its 2 million inhabitants there was not a surgeon who had seen or recalled a case of recovery after a wound of the heart. At a later date, commenting on the surgery of warfare in Portugal, Spain and France, Guthrie[26b] in 1855 writes "that the heart when wounded is capable of recovery by the permanent closure of the wound, in a few rare instances, is indisputable; and it would seem, from a consideration of the different cases which have been recorded, that such recovery takes place in consequence of there being but little blood discharged through the wound, or into the pericardial cavity, or into that of the pleura. The absence or the cessation of the hemorrhage by the contraction of the wound, or the formation of a coagulum, is the first step toward a cure. . . . If all the circumstances be considered, there can be no doubt of the propriety of closing the wound in the first instance, if the flow of blood be excessive and appears likely to endanger life. . . . When the sufferer has recovered from the imminent danger attendant on the infliction of the injury, and the pericardium is believed to be so full of blood as to prevent in a great measure the movements of the heart, it has been proposed by Baron Larrey to open the pericardium."

Early experimental studies on the heart revealed many important observations. One of these by Morgagni[34] in his *De Sedibus et Causis Morborum,* in 1761, showed that a puncture of a coronary artery might cause a hemorrhage into the pericardial sac and so compress and arrest the heart. In 1882, Block[8] sutured heart wounds in rabbits. In 1895, Del Vecchio[18] made a wound in the heart of a dog and successfully sutured the wound. Following this successful operative procedure, he suggested that the method should be adopted in operations on man. Thus experimental evidence indicated that a wound in the cavity of the ventricle could be successfully sutured and that blood effused into the pericardium would embarrass the action of the heart unless it was removed. In 1919, Warbasse[45] following experiments on dogs suggested that the apex of the heart be pulled forward by a fixation stitch to control the bleeding by compressing the great vessels at the base, keeping the heart empty and the operation relatively bloodless.

Suture of the heart in the human was carried out by Cappelen[11] by Farina[23] of Rome, and by Rehn[37] of Frankfurt in 1896. The cases of Cappelen and Farina died $2\frac{1}{2}$ and 5 days after operation respectively. Rehn's case was recovering well on the 14th day. A description of their cases follows: Cappelen's case was a man, age 24, who was stabbed in the fourth left interspace in the mid-axillary line. He went home following the stab wound and about 1 hour afterwards was found lying in a pool of blood. He was unconscious and pulseless but his heart sounds were audible. At operation the pericardium was found distended with 1400 cc. of blood. The 1 cm. wound in the pericardium was enlarged and a 2 cm. wound was found in the ventricle. The wound was

sutured and a bleeding artery on the heart tied. The patient lived $2\frac{1}{2}$ days, dying of septic pericarditis.

Farina's case was a man, 30 years of age, who received a blow from a fine, sharp dagger in the left fifth intercostal space in the parasternal line. The wound in the ventricle was oblique, from above downward and 7 mm. long. The wound was repaired with interrupted silk sutures. On the 5th postoperative day the patient developed pneumonia and died 3 days later. At autopsy the heart wound was found healed.

In Rehn's case, the patient was stabbed in the left chest with a table knife. He exhibited signs and symptoms of tamponade. On the following day, Rehn relieved the tamponade and sutured the lacerated heart. On the 14th postoperative day the patient was in good condition.

The first case of gunshot wound of the heart with an attempted repair as recorded by Vaughan[44] is that by Marion in 1898. This was a through and through perforation of the right ventricle from a pistol ball. The anterior wound of the heart was sutured but the patient died on the operating table. The first successful repair of a gunshot wound of the heart, according to Vaughan,[44] is recorded by Launay in 1902. In his case the left ventricle had a through and through perforation. Both perforations were closed, drains were placed in the pericardium and the pleura and the patient recovered.

Since the turn of the century there have been many successful cases reported in which the injured heart was repaired. Despite advances in surgery the mortality from wounds of the heart is as expected, quite high. The following series of statistics on penetrating wounds of the heart indicate the seriousness of such cases.

Author	*Year*	*No. of cases*	*Mortality*
Vaughan[44]	1909	150	65.0
Touffier[40]	1920	350	49.7
Cutler[17]	1932	28	22.4
Bigger[4]	1932	53	26.5
Bigger[5]*	1939	141	50.0

* Report by Bigger includes cases from members of American Association for Thoracic Surgery, American Surgical Association, and Southern Surgical Association.

In our own series of cases from the Detroit Receiving Hospital there were 27 cases of penetrating wounds of the heart, 21 cases were operated upon, 16 lived, a mortality of 23.8%. In addition, there were 6 cases, 3 of which were simply observed, and aspiration of the pericardium was performed in 3 others. The mortality in this group was 6%. Of the entire group of 27 cases cared for from 1939 to 1944, the mortality was 22.2%; there being 21 cases which lived, and 6 died. Of the injuries, 25 were stab wounds by knives or ice-picks; the remaining 2 were gunshot wounds.

Pathologic Physiology. The filling of the heart depends on the fact that the pressure within the great veins is slightly higher than that in the right auricle during diastole; the greater the pressure within the large veins the more rapidly will the blood enter the heart. The filling of the right auricle may be impeded by anything which hinders the expansion of the heart, such as the presence of fluid in the pericardial cavity. This can be shown experimentally, or as a result of fluid in the pericardial sac. Increasing the pressure within the pericardium and thus interfering with the venous return increases the pressure in the vena cava. Owing to the resistance offered by the pericardium, which is a tough fibrous inextensible

sac, the increase in venous pressure may be unable to force blood into the heart. When the pressure of the fluid in the pericardial cavity is sufficient to prevent blood from entering the heart, death ensues.

The effect of penetrating wounds of the heart varies with the size of the wound, its character, direction, heart chamber involved, associated coronary artery involvement, and area of confinement of the blood. Simple myocardial wounds or lacerations of the coronary vessels may cause death by direct hemorrhage producing heart compression in the closed pericardium. When larger branches of the coronary arteries are involved in the trauma, secondary myocardial infarction may be expected. Wounds of the auricles are considered more dangerous because of continued bleeding, as the auricles are thin-walled and possess less power of contractility. Wounds of the ventricles are less dangerous, especially the left. The thickness of the ventricular wall and the columnæ carneæ favors thrombus formation.

In wounds of the heart, as in other vascular injuries, hemostasis is frequently obtained by the formation of a thrombus which may plug the wound for a variable time after the injury. As arterial pressure increases, the clot may be released by the slightest exertion and thus death may occur a few days after the patient is apparently doing well. It has been shown clinically[1,31a] that especially in the ventricles, the thrombus remains and organizes, as a rule, leaving a relatively thin cicatrix in the region of the epicardial opening. The remaining part of the wound tract, instead of healing may persist as an open space connected with the heart chambers and lined by endothelium. Thus a false sacculated cardiac aneurysm may occur.

Sir George Henry Makins,[30] in 1920, in reviewing specimens of penetrating wounds of the heart noted in some that there was little evidence of hemorrhage into the pericardial sac. In these instances the wound in the wall of the heart became closed by thrombus formation. Constantini and Mocquot[14] refer in particular to delayed symptoms in 11 cases of wounds of the left ventricle. In these cases hemopericardium occurred some time after injury.

Vance,[43] in 1925, refers to 2 cases which at autopsy showed that healing may occur without operative interference. In his first case a bullet had cut a tunnel in a segment of heart muscle with little bleeding, death being due to pneumonia and spinal cord injury. In the second case, the heart and aorta were penetrated by a small bullet, the patient experiencing no trouble until 8 days afterward when the edges of the wound in the heart were suddenly forced apart and death resulted from tamponade.

Long,[28] in 1925, discussed at some length the mechanism of the production of tamponade. The possible mechanisms of closure of the parietal pericardial opening which prevents blood from escaping are: "(1) A clot which is effective only when the blood pressure has fallen very low as a result of shock or hemorrhage. (2) Displacement of the myocardial opening so that it does not coincide with that in the pericardial. This occurs somewhat at each heart beat, and as hemopericardium is increased, the relation of the openings is further changed because the blood collects in the lateral and posterior recesses, thus crowding the heart forward against the anterior portion of the sac. The greater the pressure behind the heart, and the less complete the diastole and systole, the more completely is the pericardial opening occluded; if it is in the anterior portion of the sac. (3) A small puncture of the pericardium may accompany an extensive myocardial opening, as, for example, impalement by a hatpin, upon which

the heart, by its own contractions, tears itself. (4) Heart tamponade is relatively more common and develops more rapidly in those cases in which neither pleural cavity is opened. The usual sliding of tissues obstructs the outlet." If an opening in the pericardium is large and it connects with the pleural cavity, tamponade will not occur. The patient will exhibit signs of hemorrhage and will have blood in the pleural cavity.

Cohnheim,[13] in 1881, stated that the ligation of one of the coronary arteries induced immediate and fatal arrest of the heart in the dog. That this is incorrect is well borne out by clinical and experimental data. Porter,[36] in his exhaustive research on dogs, showed that the fatal result in coronary artery ligation depended on the size of the artery. He performed a series of ligations on dogs; arrest never being observed after ligation of the septal branch alone; rarely observed (14%) with the right coronary artery; more frequently (28%) with the descending branch of the left coronary; and with the greatest frequency (64%) if the circumflex branch of the left coronary was ligated. It is also evident that the resulting disturbances are less dangerous if these vessels are ligated at a distance from their origin. These factors can only be accounted for by the presence of a collateral circulation. Elkin[22] had a case with severed coronary artery and the patient recovered. Electrocardiographic evidence of coronary occlusion did not appear until 36 hours after the accident.

Classification of Heart Wounds. The following classification of wounds of the heart is a modification of that presented by Bigger[5] and Mayer.[32]

Heart wounds may be classified into four groups:

Group I. Cases with gunshot and other large perforating wounds which produce severe injury.

Group II. Cases with a lacerated epicardium only or a lacerated epicardium plus an incomplete laceration of the myocardium.

Group III. Cases in which the missile has entered the chambers of the heart or a coronary vessel has been lacerated.

Group IV. Cases with a pericardiopleural communication.

Symptomatology and Physical Findings. In Group I the injury is usually so severe that death occurs before surgical aid can be given.

In Groups II and III the findings and symptoms are variable, depending upon the amount of bleeding and the rapidity with which tamponade occurs. Many of these cases show satisfactory progress without surgical intervention other than aspiration of the pericardial sac.

The only physical signs which provide a definite diagnosis are those of heart tamponade. The presence and position of the wound are usually such as to suggest cardiac injury. In tamponade, the circulatory collapse is out of proportion to the blood loss. There is respiratory distress and pallor with cyanosis. The blood pressure is usually low and may not be obtainable, but if it can be measured, the pulse pressure is apt to be lower than is found even in the case of massive hemorrhage. Early the pulse rate is slow, but when tamponade persists for several hours, the pulse rate increases. Physical findings over the pericardium such as increased dullness and distant heart sounds, as well as venous stasis with distention in the neck and arm veins, is an aid in the diagnosis. The presence of a water bottle contour to the heart shadow with diminution of the action of the heart as noted by fluoroscopy tends to confirm the diagnosis of tamponade.

In Group IV, with the pericardiopleural communication, there is a constant leakage of blood into the pleural cavity. The patient usually shows evidence of shock from marked hemorrhage. There is pallor without

cyanosis. The pulse is soft and rapid, and the blood pressure may be low or absent. There is profuse sweating and the body is cool. Consciousness is usually lost. It is in this group of cases that the diagnosis is frequently most difficult to make.

Treatment. In 1868, Fischer[24] collected from the literature a series of 452 cases of wounds of the heart with a mortality of 85%. The treatment employed at that time was rest, venesection, application of leeches, and occasionally, when possible, the passage of a catheter or sound into the wound for evacuation of fluid from the pericardial cavity.

In 1894, Del Vecchio[18] following experimental work on dogs doubted the necessity for operative interference in the treatment of tamponade. He states, "death in cases of wounds of the heart seems to be chiefly due to pressure from the blood effused into the pericardial sac. Since this pressure is also a check to further hemorrhage, it is a doubtful question whether operative interference may not do more harm than good as far as the hemorrhage is concerned. Paracentesis may, however, be practiced to be followed if necessary by free incision of the pericardium."

In 1928, Cox[15] used a needle successfully to aspirate the pericardial sac following the reaccumulation of fluid postoperatively. In 1933, Singleton[39] discussed a case in which 250 cc. of fluid was aspirated, and states, "following this the patient which had been moribund became tranquil, felt comfortable and the circulation returned to normal. Without prompt relief from aspiration the patient would have died from heart compression." Beekman[3] in the same year aspirated 100 cc. of blood and relieved the tamponade immediately; 9 hours later, however, the tamponade recurred and the patient was operated upon and recovered.

From the above it is obvious that every person with cardiac tamponade need not be operated upon, as also stated by Blalock,[7] and by Graham, Bigger, Churchill and Eloesser.[42] This operation becomes imperative if tamponade persists. The aspiration of blood from the pericardial sac may be a life-saving procedure to reduce intrapericardial pressure temporarily in those cases in which the patient has not been seen until a marked degree of cardiac tamponade has developed. Time may be obtained to make such preparations as are necessary for surgical intervention and the patient's condition improved by aspiration. The fact that Fischer,[24] in 1868, reported an 85% mortality, and McGuire and McGrath[29] as late as 1937 a mortality of 82% in cases not operated upon, does not presuppose that conservative therapy is contraindicated in cases with tamponade when associated with watchful waiting and aspiration of the pericardial sac.

In those cases with persistent bleeding and with pericardiopleural communication, operative intervention becomes imperative. In those cases with resulting tamponade, the blood should be aspirated from the pericardium by the costo-xyphoid route. If there is a recurrence of tamponade then exploration and cardiorrhaphy should be performed. Pericardiocentesis is an important adjunct in the treatment of cardiac wounds where tamponade is present. This simple form of therapy has too often been neglected.

According to Blalock,[6] if intravenous fluids are given when tamponade is present, the blood pressure is not increased and the patient is not appreciably improved. From our experience in patients with tamponade, if blood is forced into the veins rapidly there is temporary improvement in the blood pressure.

Choice of an Anesthetic. Either local or inhalation anesthesia can be used for repair of heart wounds. Local anesthesia is more time-consuming. In addition, in patients who are alcoholic or uncoöperative, the operation is associated with greater difficulty under local anesthesia. Frequently when the pleural cavity is opened, the difficulty in controlling mediastinal shift and collapse of the lung is so great that successful continuation of the operation is impossible. In inhalation anesthesia the procedure can be carried out with more efficiency and increased rapidity, and in cases where the pleura is opened, positive pressure anesthesia is a great aid. Operation on a moribund patient without anesthesia should not be attempted as has been suggested. The same principles should pertain in cardiac injuries as in other acute surgical conditions. In the case of a moribund patient with tamponade, aspiration of the pericardial sac will decrease the surgical risk, and in cases where there has been marked blood loss, restoration of blood volume by transfusion is important.

The Operative Treatment of Cardiac Wounds. The techniques for operative approaches to the heart are many. Variation in the approach will depend on the pathology involved. In this paper we wish to include only a brief résumé of methods as related to the approach and repair of cardiac wounds. More comprehensive surveys are to be found in articles by Cutler and Beck,[16] Matas,[31] and Shipley.[38]

Of the various methods, two types suffice:

1. Parasternal incisions: These incisions are usually on the left side and may or may not enter the pleural cavity. They are grouped by Matas[31] as follows:

(*a*) Simple intercostal incisions which do not involve the bony thorax and include only the soft parts.

(*b*) Thoracotomy with excision of the costal cartilages and ribs.

(*c*) Osteoplastic flaps which contain sections of both cartilages and ribs. These flaps may be in any direction and contain either the entire thickness of the wall *en masse*, or in layers.

2. Median thoraco-abdominal incision of Duval-Barasty,[21] as used by Milton,[33] and Beck.[16] The median incision not only exposes the heart completely, but also protects the pleural cavities. However, in traumatic wounds where time is usually an important factor, the median incision will be found to be time-consuming.

The parasternal incision we have used in our cases, whether transpleural or extrapleural, is as follows: A horse-shoe shaped incision is made over the left chest extending along the course of the third rib from the nipple line to the sternal margin. The incision is then carried along the left sternal margin to the fifth costal cartilage where it again extends to the nipple line over the fifth rib. The skin and pectoralis muscles are brought up in one flap exposing the costal cartilage and portions of the ribs. The costal cartilages of the third, fourth and fifth ribs, as well as portions of these ribs are removed, leaving the periosteum and perichondrium behind. If the pleura was previously opened by the stab wound, it is further incised exposing the pericardial sac. If the pleura is intact, it is gently pushed away from the pericardial sac, thereby eliminating the danger of injury to the pleura during the operation.

In most of our cases the heart has been exposed through a transpleural approach, under positive pressure anesthesia. This incision has allowed ample room for suture of the injuries to the left auricle and ventricle and in most cases of the right ventricle. In one instance, with a gunshot wound of the right auricle, a right parasternal incision was used.

Many transpleural approaches were formerly discredited because of the risks and danger of the sudden admission of air into the pleural cavity. The use of positive pressure insufflation has diminished the operative risk. When the pleura is not involved, and there is no pneumothorax, opening the pleural cavity increases the operative risk moderately and should be avoided if possible.

The pericardial sac, which has been thus exposed, is opened and the blood evacuated. There was little or no bleeding from the heart wound at operation in several of our cases when the ventricle alone had been perforated. Interrupted sutures of silk were used to seal the wounds, the long ends of the suture being gently used to steady the heart. The "control suture" in the apex as used by Warbasse[45] in his experiments on dogs and more recently by Cutler and Beck[16] were also used in a number of our cases. It should be pointed out, however, that if too great a traction is used on the control suture there will result persistent, even though slight, bleeding.

In those cases in which a large defect in the heart is seen through the pericardial sac, the pericardium can be utilized to plug the opening and prevent the intermittent gushing of blood from the wound. The pericardium can then be incised a short distance from the control pressure point and the wound sutured.

Pericardiocentesis has been performed for some time for diagnosis of pericardial effusion as well as for decompression in infectious processes. It has likewise been used in hemopericardium from traumatic heart wounds. Matas[31c] referred to this procedure as a form of treatment of traumatic wounds of the heart with hemopericardium. This form of treatment has not been used as frequently as it should for fear of wounding the heart or coronary vessels with serious consequences. In the interest of obviating such dangers, many and varied types of needles or trocars have been devised. The site chosen for the introduction of the exploring needle should not injure the mammary vessels, pleura or the heart and at the same time provide a certainty of reaching the large collection of fluid in the most favorable position for aspiration. Numerous sites have been advised for this procedure. There are two sites we prefer for doing a paracentesis. In the xiphoid approach the needle enters the left xiphoid space at its extreme upper edge of the chondro-xiphoid angle. This offers greater advantages and less risk than any other method. The needle is driven obliquely upward and backward at this point so as to avoid the diaphragm and enter the pericardial sac without touching the pleura or peritoneum. In the other approach we have used, the needle is inserted into the sixth left intercostal space, close to the margin of the sternum. When inserting the needle in either method, a gentle vacuum in the syringe should always be present and the patient's bed rest be in a semirecumbent position. The inability to aspirate fluid in the pericardial sac does not necessarily exclude the presence of fluid, as blood clots may be present to block the needle or the needle may not have been inserted properly.

Inasmuch as a high mortality and morbidity still exist in the care of cardiac wounds with tamponade, it becomes apparent that any procedure which can reduce this mortality should be given wider use. This is especially true when slender knives or ice picks are the causative agents. These wounds are usually 1 to 2.5 cm. in length and most often enter in an oblique direction through the heart musculature. These wounds have a tendency to seal off early with thrombus formation. This is possible when the blood accumulating in the pericardial sac compresses the wall

in the region of the wound and prevents continued bleeding. This has been a frequent observation in the cases we have explored. Following release of the tamponade during the operation, the heart was carefully examined and frequently the wound was not found until by digital manipulation the wound edges separated and some bleeding occurred. We have also observed early thrombus formation at postmortem in one of our cases under observation in which there was no tamponade present. In another case, where a bullet tunnelled the musculature of the heart, no bleeding was evident when the tamponade was released. From these observations it becomes evident that before any operative procedure is contemplated the pericardial sac should first be emptied and the patient watched for reaccumulation of fluid. It is necessary to keep these patients quiet for a few days in order to prevent the release of the early thrombus when under exertion. However, when a large object, such as a bullet, piece of shrapnel, or a wide butcher knife is the causative agent, operation will probably be the only life-saving procedure, and aspiration should be utilized to get the patient in better condition and to allow time for preparation for the operation.

In our last 3 cases of stab wound of the heart with tamponade, aspiration was the only treatment necessary. Only one aspiration was necessary and all 3 patients responded nicely.

Immediate Postoperative Complications From Heart Wounds. The postoperative complications either immediate or late may include any of the following: Coronary occlusion, pericarditis, pericardial effusion with tamponade, thrombosis with secondary emboli, ventricular fibrillation, hemothorax, hemopneumothorax, tension-pneumothorax, empyema, pneumonia, atelectasis, and bacillus gas infection.

The most important complications postoperatively in cases of cardiorrhaphy are infection and reaccumulation of fluid in the pericardial or pleural sac. If an opening is not left in the pericardium at the time of the operation, any fluid which may accumulate will not have an opportunity for exit into the pleural cavity or out through the external wound. Effusion into the pericardium is inevitable after an operative procedure on the heart and postoperative tamponade may occur if the pericardium is closed too tightly. While a drain in the pericardium may obviate this, the presence of a drain does more harm than good and should not be used.

In our experience the most frequent complications have been atelectasis and hydrothorax. We have had no cases with postoperative cardiac tamponade where the transpleural approach was used. With the pericardial sac loosely closed any drainage that takes place in the pericardial sac can escape freely into the pleural cavity. We have no cases with serious postoperative infection. Atelectasis ought to be watched for and treated early. In our series, bronchoscopic aspiration has been necessary in but 2 instances. Hemothorax and hydrothorax have been our most common postoperative complications. This has caused no serious trouble as we have resorted to aspiration of the fluid when necessary.

Late Postoperative Outlook. In 1925, Dshanelidze[19] collected 535 cases (1896 to 1921) of cardiac trauma and analyzed the late postoperative results. Operations had been done for a stab wound in 402 cases, and for projectile injuries in 133. The immediate mortality was 56%. In 96.5% of 113 cases traced for 2 months up to 18 years, the function of the heart did not seem to be impaired. Even prolonged complicating infection did not prevent satisfactory return of function. The location of the wound and operative technique seemed immaterial. The sutured heart passed

through infectious diseases, abuse of alcohol and tobacco, long operations and the strain of childbearing. The unfavorable outcome in 3.5% was due to aneurysm and adhesions.

Cecchini,[12] in 1925, discussed the follow-up study of 2 patients after a period of many years had elapsed since operation. One patient was re-examined by Cecchini who had had a stab wound of the heart sutured 17 years before, and no evidence of cardiac impairment was found. He had received a report of good health from a similar second patient.

Hesse,[27] in 1925, compared 12 cases which he had followed for long periods after suture of the heart with 107 collected from the literature. The interval since the operative procedure ranged from 2 months to 18 years. The earning capacity was unimpaired in 80.1% and only 1.7% were disabled. The ultimate outcome was excellent and the general condition good even in 9 patients who had had purulent pericarditis.

Noth,[35] of the Department of Medicine of Wayne University, has followed 8 of our cases over a period of from 5 to 36 months. Five complained of a variety of indefinite symptoms and 3 had no symptoms referable to the heart. However, the latter all had abnormal electrocardiograms, whereas 3 of the 5 patients with symptoms had normal tracings. Abnormal physical findings with reference to the heart were absent except in 1 patient with complicating hypertension and syphilis and in another who had a widely split first heart sound which coincided with prolongation of the P–R interval. No patient showed retraction of the ribs. Pulsus paradoxus was specifically noted as absent in 4 patients. Venous pressure was normal in the 7 patients examined in this regard.

It is remarkable that patients who have suffered severe cardiac wounds have so few sequelæ after recovery from their operative procedure. As a rule they are able to carry on their usual work with no impairment and from this standpoint repair of the injured heart gives very gratifying results.

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OPHTHALMOLOGY

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DRUSEN (HYALINE BODIES) OF THE OPTIC DISK

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For many years, in fact until very recently, "drusen" of the optic disk, also spoken of as hyaline bodies, colloid bodies, hyaline varicosities, granular formations, globular masses and kalkdrusen, have been regarded essentially as ophthalmoscopic curiosities. In the earlier days, when ophthalmoscopic examinations were less frequently made without some definite indication of visual or ocular disturbances, drusen, when observed, were usually regarded as a part or residual of the intraocular or optic nerve disturbance which was responsible for the loss of vision. As ophthalmoscopic studies became more universal in patients presenting themselves only for the correction of refractive errors or for general systemic and neurologic disorders, it became apparent that drusen were present at times in the optic disks of apparently healthy individuals without other recognizable intraocular disease. It seemed logical to assume then that the drusen were congenital structural anomalies without significance with respect to the diagnosis of systemic disease or to the future vision of the individual. Soon, it became obvious that in certain cases the drusen could produce or at least be associated with defects in the field of vision, and that these visual field defects might be progressive, possibly as the result of an increase in the number or size of the drusen. However, it was not until the publication of a paper by Reese[13] in 1940 that a possible systemic significance of the drusen was suggested.

Ophthalmoscopically, drusen appear usually as rounded, waxy, rather shiny or glistening, more or less translucent bodies or nodules of varying size in the substance of the optic disk. They are most or best visible as a rule near the margins of the disk and at times may seem to lie in the disk

rings or in the marginal retina or at least to overlap the margins of the disk. They are variously described as resembling frogs' eggs or tapioca grains or as mulberry-like or grape-like clusters. If numerous, they seem to impart a yellowish waxy color to the entire disk simulating that of secondary optic atrophy. This is particularly true if they lie near or on the surface of the disk. In the latter case they appear as nodular masses which may project into the vitreous; it is said as much as 14 diopters. If the drusen lie deeper within the substance of the papilla, they may cause an appearance of hyperemia or congestion of the disk with fulness and marginal blurring, and at times measurable elevation. Since such deep lying drusen are often hard to see, the diagnosis of choked disk or optic neuritis may be suggested at the initial examination. When the drusen lie mainly or extensively in the edges of the disks and overlap the marginal zones of the retina, the appearance may simulate that of peripapillary choroidal atrophy or choroiditis. Some of these various appearances have been illustrated recently in fundus photographs such as those in the articles by Reese[13] and by Rucker.[14] Rucker calls attention particularly to the field defects which have been noted from time to time by different authors as associated with drusen and probably caused by the pressure of the hyaline deposits on the nerve fibers. According to Rucker, the most characteristic field defects are enlargements of the physiologic blind spot, arcuate scotomas which may break through to the periphery or may be double and produce ring scotomas, and contractions of the peripheral fields, especially in the lower nasal quadrant. Drusen are usually bilateral but they can be or at least appear to be unilateral, since they may be very numerous in one disk and very scanty or essentially invisible in the other disk. Drusen can be observed at any age, the youngest reported case being 8 years old according to Duke-Elder,[3] who states, however, that they "are more common in the aged and in the presence of retinal disease." It is perhaps more generally thought now that drusen are primarily congenital formations though they can increase in size and number during the course of years.

According to Duke-Elder,[3] "pathologically these bodies are made up of concentric laminations with no cellular structure or capsule, and frequently showing masses of calcification. The great majority of observers agree that their basis is a hyalin-like material . . . They are associated with no surrounding inflammatory reaction." These were essentially the findings of de Schweinitz[18] who reported one of the relatively few cases in which microscopic examination was made of clinically observed drusen. He described the drusen as "compound hyaline bodies," oval masses of whitish color composed of a series of smaller bodies in which the markings with concentric lines was very distinct. He thought that the masses were probably cross-cuts of a ring of hyaline tissue with some calcareous deposits occupying the substance of the nerve head in advance of the lamina cribrosa, surrounding the central vessels, and not passing beyond the outer margin of the papilla. The optic nerve showed well-marked atrophy; but de Schweinitz did not think that this was connected with the drusen formation.

Goldstein and Givner,[6] in 1933, found drusen of the optic disk in one eye of a patient who had chronic glomerulonephritis and died in uremia. Retinopathy was present and also some atypical pigmentary deposits in the retina. Microscopically, the drusen appeared as a mass composed of concentrically arranged layers having no cellular structure or capsule. There was a definite central area of calcification and around its projecting

surface was a proliferating glial membrane which separated it from the surrounding retina and choroid. In this membrane were several discrete smaller masses of calcification. There were no evidences of inflammation. The individual components of the mass were concentrically placed laminated structures with a lumen. The authors called attention to the three outstanding theories advanced previous to this report, as to the pathogenesis of these hyaline deposits: (1) that they like the hyaline deposits in the lamina vitrea of the choroid are secreted from pigment epithelium which, in the case of drusen of the disk, has been misplaced on the papilla; (2) that they originate from exudate laid down in the nerve head by a previous inflammatory process; and (3) that they are derived from neuroglia. Goldstein and Givner favored the third theory since they found many hyaline deposits in the neuroglia itself. However, Duke-Elder stated: "All that can be said is that they seem to represent the deposition of a hyalin-like material because of some local metabolic disturbance of unknown and probably varied etiology."

In 1941, Samuels[15] reported the histopathologic characteristics of the drusen of the optic disk which he had encountered in the examination of 20 enucleated eyes, 7 of which had been removed because of secondary glaucoma. In one case, a drusen was located just posterior to the lamina cribrosa in the trunk of the optic nerve. In all other cases, the drusen were located anterior to the lamina cribrosa. Only 4 showed calcification. Samuels classified the drusen into intrapapillary, epipapillary and circumpapillary or transitional. The majority of the drusen were intrapapillary, in the middle and deeper layers of the papillæ, not near the vitreous surface. In one case, however, the drusen were on the surface of the disk embedded in a glial membrane. "Evidently these particular concretions were the product of a metaplastic process in new-formed neuroglia tissue." The glial membrane was thought to be a part of the reaction to a perforating ulcer of the cornea.

According to Samuels, drusen in the center of the papilla never show pigment. Drusen around the margin of the optic disk (circumpapillary or transitional drusen) may or may not show pigment. If they are nonpigmented, they may originate either from the papilla or from the retina. If they are pigmented, they arise from the pigment epithelium of the retina which has invaded the margin of the papilla. Samuels thinks apparently that atrophy of the optic nerve can be secondary to the presence of drusen. In his opinion drusen in the narrow unyielding sclerochoroidal canal would be more likely than those in the looser anterior tissues, to cause pressure atrophy of the nerve fibers and defects in the field of vision. He thought also that old calcified drusen might acquire a toxic and irritating effect on the nerve fibers. He regarded calcification as an indication of the greater age of the drusen.

With regard to the nature and pathogenesis of drusen, Samuels stated, "It is likely that every druse starts with a deposit of minute globules of hyaline which fuse and then increase in size by successive accessions. Separate drusen may coalesce to form large ones, which for this reason have uneven surfaces." He noted that glial cells may produce hyaline as shown by the finding of drusen in pure glial tissue on the surface of the retina and papilla. The mechanism of the formation of drusen was, he thought, an abnormal secretory activity of the glial cells of the papilla under the influence of irritation. He called attention to the fact that the papilla is particularly prone to produce drusen in pigmentary degeneration of the retina and in secondary glaucoma leading to gliosis of the retina

and he thought therefore that in many cases the drusen were the result of some local disease of long duration within the globe itself. He noted, however, that in some instances, drusen occurred in the otherwise normal eyes of young healthy individuals and he stated that "there is probably a constitutional basis for such early spontaneous growths."

It is noteworthy that, prior to the publication by Reese, no mention is made, except by Lauber,[10] in histopathologic descriptions of drusen of the optic disk of any definite associated cellular structures. Lauber noted that some large cells can be seen in close proximity to the smaller drusen. Apparently he did not attach any particular significance to these cells; but he noted some other cells which he thought were derived from the retinal pigment epithelium. Reese studied the histologic characteristics of the drusen found in the optic disks of 9 globes. Since these were found in a series of 893 enucleated eyes, Reese gives the probable incidence of drusen as 1%. This would seem to be higher than the probable expected incidence of at least ophthalmoscopically visible drusen. Five of the eyes studied by Reese were removed because of absolute glaucoma, one each because of buphthalmos, hydrophthalmos, malignant melanoma of the choroid, and traumatic detachment of the retina. Reese considered that the drusen were entirely independent of the other lesions in the eyes. They had been observed ophthalmoscopically in the optic disk of the fellow healthy eye in one case. According to Reese, the lesions were sharply demarcated, at times by a thin glial capsule. The main mass of the lesion was composed of conglomerate smaller masses with glial septa between them. Daughter lesions occurred around the main one. The bulk of the lesion was made up of calcium and an amorphous material, either hyaline or a closely related substance. Sometimes the lesion appeared to be concentrically lamellated around a central focus or to be arranged in crystal sheets. Cyst-like spaces appeared centrally in some lesions. Cellular elements were found immediately around or in the periphery of most but not all of the lesions. Cells with large oval nuclei tended to become shadow cells, then necrotic, and finally calcified within the lesion. Other cells had a large nucleus, distinct nucleolus, and a well-demarcated polygonal shaped protoplasmic border. Some of these cells contained a homogeneous refractile substance like that in the main lesion. Some of the smaller daughter areas resembled calcified cells. Reese thought that "the lesions represent a congenital excess of immature neuroglia which undergoes degeneration."

Reese noted the similarity between his findings and the histologic characteristics of the lesions found in the retina and optic disk in cases of tuberous sclerosis. Messinger and Clarke[12] studied the tumor on the optic disk in a case which showed at necropsy typical lesions of tuberous sclerosis, multiple tumors of the brain, rhabdomyoma of the heart, lipofibromas of the kidneys, adenoma sebaceum of the Pringle type, and in the right eye a single, raised whitish tumor, 3 mm. in diameter, which covered the upper and inner two-thirds of the optic disk. The tumor involved all the layers of the retina and invaded a portion of the optic nerve. In the center of the tumor was a large irregular mass of ossification and around this were concretions containing calcium. At the periphery of the tumor was a thin layer of polymorphic tumor cells with indistinct boundaries and the suggestion of a syncytium. The cells had round or oval vesicular nuclei with a single nucleolus. The cells showed some vacuolation and some thick processes, some of which contained short fine glia fibrils.

According to Messinger and Clarke, only 4 histopathologic descriptions

of the retinal or disk lesions in tuberous sclerosis had been published previously. Schob[17] considered them to be gliomatous tumors. Feriz[4] called them atypical neuroglia-like tissue. Kuchenmeister[9] found cells of varying type and shape and new-formed glial fibers. Van der Hoeve[19] suggested that the cells were descendants of the first anlage of the retina, neurocytes which had not differentiated into glia or ganglion cells or "glia neurocytes." He presumed that the tumors originated from embryonic cell rests and called them phakomata. In Messinger and Clarke's case, Ida Mann thought that the tumor developed or began to develop during the second stage of retinal differentiation (between the 6th week and the 3rd month of embryonal development) from glia cells of the inner neuroblastic layer with possibly a few undifferentiated ganglion and amacrine cells included. Messinger and Clarke were inclined to classify their tumor as a gliomatous hamartoma. Koch and Walsh[8] expressed the opinion that "the disease entity, tuberous sclerosis, appears to be the result of a developmental anomaly commencing early in fetal life and eventuating in widespread metaplasia which affects chiefly the ectodermal tissues but with subsequent prevalence of both mesodermal and entodermal derivatives."

Grinker[7] had suggested that the retinal tumors in tuberous sclerosis were probably astroblastic neoplasms of low growth potentialities. Tarlan stated that, in collaboration with McGrath, he had found, in a tumor of the optic nerve in a case of tuberous sclerosis, glial fibrils, absence of neurofibrillæ and typical perivascular feet. He considered that these findings proved that the tumor was an astroblastoma. He thought that the cells found by Reese bore a striking resemblance to astroblasts and he said, "While it is of course true that there is an urgent need for careful histologic study with differential staining, the evidence at hand certainly suggests that Dr. Reese's tumors are also astroblastic neoplasms of low growth potentialities and that they are at least related to, if not identical with, the manifestations of tuberous sclerosis." Reese himself thought that aside from the bone formation, his cases of drusen presented the same pathologic picture as that described by Messinger and Clarke in their tumor of the disk. Verhoeff[21] has noted ossification in drusen of the disk. Clinically, there is undoubtedly considerable similarity in appearance between hyaline bodies and the nodules making up the retinal and disk masses in tuberous sclerosis.

Reese concluded that "the findings in this study indicate that drusen of the optic nerve are a feature of the congenital developmental anomaly known as tuberous sclerosis. They may appear as a part of the fully developed protean disease but more frequently are seen as one of its many clinical variants or formes frustes." He stated that van der Hoeve[19] found a typical retinal tumor without any other manifestation of the disease in one member of a family in which siblings had had typical tuberous sclerosis. The classical clinical picture of tuberous sclerosis is mental deficiency, epilepsy, and adenoma sebaceum. Reese called attention to the well-recognized fact that disorders of the nervous system of one sort or the other are rather common in individuals who show drusen in the optic disk. In 18 of the 54 cases reported in the literature which Reese reviewed, there were mentioned such findings as convulsions, psychosis, disturbances of gait or speech, hydrocephalus, or papilledema. Renal dysfunction was noted in 7 cases, heart disease in 2, other congenital anomalies of the eye in 5, and retinitis pigmentosa in 7 cases.

Though instability of the nervous system is often striking in individuals

presenting drusen of the optic disk and in members of their immediate family, it must be remembered that actual organic cerebral disease of the type seen in tuberous sclerosis has not as yet been definitely demonstrated in association with typical simple drusen of the disks. Small areas of cerebral calcification such as are seen in roentgenograms of the head in cases of tuberous sclerosis have not been demonstrated in association with drusen. Among the 3 clinically observed cases reported by Reese, examination of the nervous system was not carried out in 1 and yielded negative results in 2. Roentgenograms of the head were negative in 2 cases and a ventriculogram was negative in 1. Pneumoencephalograms were negative in 2 cases reported by Schlezinger, Waldman and Alpers.[16] In one of these cases, an electroencephalogram showed showers of sharp and slow wave formations in the left frontal and parietal areas which were of questionable significance.

Electroencephalograms have been done at the Mayo Clinic on 6 patients who had drusen in the optic disks. The results were interesting though probably not clinically significant. Two were reported as essentially normal. In one of these patients, an electroencephalogram done previously elsewhere was said to show some dysrhythmia. At the time of our examination there was slight delta activity in the right temporal area. In a third patient who presented a post-head injury syndrome, the electroencephalogram gave a low potential record but was otherwise negative. A pneumoencephalogram was normal. In the fourth case, the electroencephalogram showed some dysrhythmia; in the fifth, dysrhythmia and bilateral occipital delta activity Grade 1 to 2, and in the sixth, generalized dysrhythmia. The fifth patient, in whom the drusen were unilateral, had no presenting complaints except myopia. The electroencephalographic findings, the appearance of the optic disks, and the field defect, an inferior arcuate scotoma, had remained unchanged at the end of 9 months. In all these cases except the sixth, roentgenograms of the head were normal. In the sixth case, the sella was enlarged and the dorsum eroded. In 3 of the cases, examination of the central nervous system was objectively normal. One of the patients presented an Adie's syndrome, one had syphilis of the central nervous system with positive serology in the spinal fluid, and the sixth had, along with emotional instability, signs of an organic brain disorder of indeterminate nature mainly in the cerebellum.

So far as I have been able to determine there have been no reports in cases of drusen in the disks of histologic changes in the brain similar to those found in tuberous sclerosis. In Lauber's case, the brain was said to be normal; the optic nerve was atrophic. In the case reported by de Schweinitz,[18] the patient had had mental symptoms and the brain was said to show ependymitis with ventricular dilatation. The optic nerves were atrophic. However, there were no histopathologic changes demonstrable in the brain substance or in the other cranial nerves. In de Schweinitz's opinion, the negative findings in the brain and in the other cranial nerves indicated that the formation of drusen in the optic disk is a purely local process, the nature of which is unknown. He did not think that the drusen were produced by the process which caused the atrophy of the optic nerves.

As noted by Reese,[18] tuberous sclerosis is a heredofamilial disease. Duke-Elder states that it has been observed in identical twins and that it has been reported in three generations of one family. Drusen of the optic disk also have been observed to have familial and hereditary incidence. Lauber[10] observed drusen of the disk in a mother and 2 daughters. Ancke[1]

found them in several members of two families in association with retinitis pigmentosa. On the basis of his observations in two families, Braun[2] considered the tendency to drusen formation to be an hereditary dominant. He found drusen in a mother and one daughter and one son. In the other family group reported, the findings were somewhat questionable. Leimgruber[11] reported his observations on drusen of the optic disks among the members of five families. In Family 1, drusen were found in 6 out of 9 sisters and brothers and also in 2 of their children. In Family 2, drusen were seen in 2 sisters; in Family 3, in 2 brothers, and in Family 4, in identical twins. In Family 5, a woman and her son were affected.

Although it cannot be considered to be definitely proved at present that drusen of the optic disk are really slow growing astroblastomas of hereditary and familial occurrence and that they represent a variant of tuberous sclerosis, the evidence presented is at least suggestive and intriguing and warrants further study and investigation. For as Reese points out, "If this conclusion is correct, drusen of the optic nerve assume new significance as a familial developmental defect which is frequently associated in the patient, in his progenitors, in siblings, or in offspring with serious involvement of the central nervous system, and rarely, with renal and cardiac lesions."

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BOOK REVIEWS AND NOTICES

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, Univ. of Maryland; Assistant in Gastroenterology, Mercy Hospital; Consulting Roentgenologist, Sinai Hospital. Second Ed. Pp. 769; 550 figs. Baltimore: Williams & Wilkins, 1945. Price, $7.00.

THE 2nd edition of this book is exactly what its title indicates. The author has provided in a unique way not only pertinent roentgenologic diagnostic criteria but has included the clinical considerations as well. Such a book is of extreme value not only to the clinician doing his own Roentgen studies of the gastro-intestinal tract but to the medical radiologist as well. In almost every lesion the author considers the incidence, the etiology, symptoms, pathologic manifestation of the primary lesion and any complication thereof. Such a book provides for the radiologist a quick reference book and the book can be resorted to as a reference book in the true sense of the word. The author has quoted from many publications.

The book is profusely illustrated and there are a number of pen and pencil drawings. Likewise the author has included in addition to the usual and more frequent gastro-intestinal lesions, a number of the various anomalies and rare conditions.

The publisher is to be congratulated on the type of paper that has been used and the excellence of the printing and illustrations. E. P.

PENICILLIN THERAPY Including Thyrothricin and Other Antibiotic Therapy. By JOHN A. KOLMER, M.S., M.D., DR.P.H., SC.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple Univ.; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology, Graduate School of Medicine, Univ. of Pennsylvania. Pp. 302; 22 figs. New York: London: Appleton-Century, 1945.

Now that penicillin has become available commercially as a therapeutic agent, there is a need for a clear statement of its pharmacodynamics, the indications and contraindications for its use, and the methods available for its administration. Dr. Kolmer's book fulfils this need as well as our present knowledge permits. As he points out, it is amazing and pleasant to realize that penicillin has progressed in 4 years from a bacteriologic curiosity to the most powerful weapon of the modern therapeutic armamentarium. In the monograph, his approach has been a review of all of the most important articles in the literature on the subject of penicillin. Coverage of the literature has been complete but not redundant, ranging from a consideration of the optimal media on which the mold has been grown to the manifold clinical uses of penicillin. Dr. Kolmer's review is completely up-to-date, as is shown by his inclusion of the latest literature on the oral administration of penicillin and on penicillin F., G., and X. with references as late as 1945.

This work is of especial interest to laboratory men, since all of present acceptable methods of detection and assay have been well described, and he has discussed those physical and chemical properties that necessitate special handling of the drug.

Most clinicians are well aware of the more important indications for the use of penicillin, but the modes of administration other than intramuscular are often seriously neglected. Examples of this are the failure to use intrapleural penicillin in empyema and intracisternal penicillin in the severe meningitides.

These techniques along with proper dosage schedules are thoroughly covered. As indicated by the title, the book includes an adequate account of the other important antibiotics such as streptomycin and thyrothricin now under experimental and therapeutic consideration.

Dr. Kolmer's work provides an excellent summary of a field in which the accumulated literature has become too voluminous for most of us to cover. This volume should be of great importance to all medical men whether they be students, general practitioners, surgeons, internists or laboratory men.

R. M.

MASS RADIOGRAPHY OF THE CHEST. By HERMAN E. HILLEBOE, M.D., Medical Director, Chief, Tuberculosis Control Division, U. S. P. H. S.; Professorial Lecturer on Tuberculosis Control, George Washington Univ. School of Medicine, Washington, D. C.; and RUSSELL H. MORGAN, M.D., Surgeon (R), Medical Officer-in-Charge, Radiology Section, Tuberculosis Control Division, U. S. P. H. S. Pp. 288; 93 figs. Chicago: Year Book Publishers, 1945. Price, $3.50.

THIS little manual of 13 chapters is one of the real contributions to medicine. Although our knowledge in tuberculosis has increased in many ways, no real contribution has been made in the field of prevention. There is no specific cure or any effective immunizing agent against the disease. The development of mass radiography of the chest has provided a method whereby it has become possible to discover the sources of the infection and thereby render it possible for each community to make a direct attack upon the tuberculosis problem.

There are no two men in the world who have contributed more to this subject and to the development of the methods of mass radiography than have Drs. Hilleboe and Morgan. Through their intelligent efforts, the world is being provided with a program which should largely eradicate tuberculosis.

For anyone interested in this subject, and it should be of interest to all medical men as well as all public health physicians, Drs. Hilleboe and Morgan have, in a comprehensive way, written an effective manual on the objectives of tuberculosis control; the community planning of such a program; considerations about the equipment to be used; the Roentgen technique of a mass radiography; considerations concerned with the Roentgen diagnosis of lesions in the chest and other important items concerned with such an undertaking.

Some of these observations have been made by others as well as by the authors; but for the most part, this manual is the first comprehensive treatise on this subject and one finds it difficult not to be too enthusiastic.

The publisher is to be congratulated on the general make-up of the manual, the illustrations, the paper and the printing. This is a book that should be of interest to every physician.

E. P.

THE NEW-BORN INFANT. A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale Univ.; Attending Obstetrician and Gynecologist to The New Haven Hosp. Third Ed. Pp. 314. Philadelphia: Lea & Febiger, 1945. Price, $3.25.

THIS handy monograph discusses clearly and comprehensively the problems of nursing care, feeding and feeding disorders, birth injuries, infections and disorders of specific organ systems as they present themselves in the neonatal period. The contents are well organized and up-to-date and reflect the modern point of view. One may question the propriety of advocating toilet training as early as 2 weeks of age, or of giving the vitamin C content of orange juice in terms of "units" rather than milligrams. This edition appears to have gone to press prior to the discovery of the relationship of maternal German measles to infantile malformations and of prematurity to eye lesions; but the Rh factor and the relationship between diabetes in the mother and cardiac enlargement receive specific mention.

Every obstetrician, pediatrician and general practitioner who assumes responsibility for the care of newborn infants, whether in nurseries or private homes, should have at his finger-tips the information contained in this handy volume. I. W.

MARIHUANA PROBLEMS—in the City of New York. Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana. Pp. 220. Lancaster: Jaques Cattell, 1944. Price, $2.50.

THIS monograph is the result of a study carried out by the Mayor's Committee of the City of New York in response to rumors that marihuana smoking was common among large segments of the city population and was even indulged in by school children. The study reveals that the assertions leading to the study were exaggerated; but the medical profession and the general population have profited by a serious investigation of the sociologic, medical, psychologic and pharmacologic features of marihuana smoking. Among the significant conclusions of the study are that marihuana smoking does not lead to addiction in the medical sense of the word; that it does not lead to heroin, morphine or cocaine addiction; that it is not the determining factor in the commission of crimes; that it is not widespread among school children; and that juvenile delinquency is not associated with the practice of smoking marihuana. Body steadiness and hand steadiness are most seriously affected by the drug. Psychologic studies reveal that marihuana induces feelings of relaxation, disinhibition, and self-confidence. The studies of the pharmacologic action of the drug are extensive and well done.

The investigation has been thorough and inclusive and constitutes a serious contribution to the effects of marihuana on the body and emotions. It can be recommended highly to social workers, physicians, and lay readers.

INFANTS AND CHILDREN. Their Feeding and Growth. By FREDERIC H. BARTLETT, M.D., Attending Pediatrician, Babies' Hosp., New York City. Sixteenth Ed. Pp. 428. New York: Farrar & Rinehart, 1945. Price, $2.00.

ANY book for parents which passes through 16 printings in 13 years must have a popular appeal and meet a mass need. This well-known one by Bartlett is full of instructions on the common every-day problems of infant and child rearing. Its distinctive quality is its lively conversational style. The information is broad in scope and sound in character, yet not so meticulous and detailed that the layman will be tempted to use it as a substitute for skilled medical supervision. I. W.

THE EXAMINATION OF REFLEXES. By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. Pp. 222. Chicago: Year Book Publ., 1945. Price, $2.50.

A SYSTEMATIC synthesis of some of the numerous deep muscle reflexes is presented. Twenty-five muscle reflexes are critically described and discussed, from the orbicularis oculi reflex to the distant toe flexor reflex. The author's basic principles are as follows:

The most important reflexive stimulus for the muscle consists of a sudden, brief concussion and stretching of the muscle tissue. The contraction of a muscle on being stretched may exist in latent form and become apparent only when there is a functional or an organic increase in muscle tonus. Since concussion of the muscle and its stretching constitutes the true cause of the deep muscle reflex, the point from which the response may be achieved is not essential. Every muscle crosses one or more joints and is comparable therefore to a tautly-drawn bowstring. Sudden stretching of such a string may be achieved by a force acting either on the plane or on the convex side of the bow mechanism. Therefore, the possibility of elicitation of a deep muscle reflex by striking the bone offers much to the comprehension of many misun-

derstood and misnamed reflex phenomena. The transmission of concussion through the bone makes it understandable that under favorable conditions a single tap with the reflex hammer may affect several functionally different muscles and thus evoke multiple, but completely independent, unrelated reflexes. A reflex should be named according to the acting muscle, not according to the point of stimulation. For a given reflex the muscle is always the same, but the place of stimulation may vary considerably. The term tendon reflexes should not be used because stimulation of the tendon cannot evoke any reflex action unless the muscle tissue is influenced through the tendon. There is no such thing as a tendon stretch reflex. The same applies to so-called bone, periosteal, osteoperiosteal, osteo-tendon, joint, fascial reflexes. Reflexes which do not fit into the regular reflex pattern are often called paradoxic, inverted or antagonistic. There is nothing paradoxic about them; they are simply occasional forms of well-known deep reflexes appearing under certain conditions and depending on particular techniques applied in their elicitation.

In the foregoing manner, Dr. Wartenberg indicates the premises on which his physiologic approach to the muscle reflex problem is made. Carefully worded description of method and technique is adhered to throughout the monograph. Every student of the subject should find the book interesting, stimulating and thought-provoking. A. O.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By Frank R. Ford, M.D., Associate Professor of Neurology, Johns Hopkins Univ. Second Ed. Pp. 1143. Springfield, Ill.: Thomas, 1944. Price, $12.50.

In its new and expanded form, Ford's text-book maintains its preëminent position. Every disease of childhood which may have nervous system complications is specifically mentioned, and of course those conditions which are primarily neurologic in character receive full discussion. Child psychiatry is wisely not included. The classification of subjects is by etiology rather than by organ systems, with 2 excellent introductory chapters on examination and clinical anatomy and physiology. Every doctor—whether pediatrician, neurologist, internist or general practitioner—who has to cope with child patients ill with nervous system diseases, would be wise to own and use this book as a desktop reference. I. W.

Foster Home Care of Mental Patients. By Hester B. Crutcher Director of Social Work, State of New York, Department of Mental Hygiene. Foreword by Arthur H. Ruggles, M.D. Pp. 199. New York: Commonwealth Fund, 1944. Price, $2.00.

This unusually valuable treatise tells how the mentally ill may receive excellent extramural care. Two methods are employed: the colony plan and the district plan wherein the patients are scattered. The sites of choice for foster homes are small towns or suitable country locations. The various chapters discuss Family Care: Its Meaning and Values; Administration and Results of Family Care; Family Care as a Therapeutic Procedure; Selection of Patients; Selection of Homes; Supervision of Patients; Two Methods of Organizing Family Care; Some Case Histories; Suggested Forms and Procedures.

There is also an Appendix on Family Care Programs in the United States. Patients may be selected from the præcox group; senile subjects who only require individual attention and kindness; those whose dissatisfactions with hospital treatment decrease with family care; those unable to adjust outside the hospital; those with paranoid trends impossible to adjust among former associates; those having emotional needs met and security somewhat restored by family care. Among those who should not be permitted such freedom are subjects who become excited, noisy and violent, suicidal, homicidal, those

with erotic tendencies or who attempt to escape, and alcoholic and narcotic addicts. To the colonists come the advantages of home comforts, normal associations, greater freedom and suitable work. The foster families obtain fuller economic security. Fewer buildings would lessen the taxpayers' burden. Still another advantage—promotion of a better understanding among the public toward mental patients, of whom it is sometimes too fearful.

N. Y.

IMMUNO-CATALYSIS. By M. G. SEVAG, PH.D., Assistant Professor of Biochemistry in Bacteriology, Department of Bacteriology, School of Medicine, Univ. of Pennsylvania. With a Preface by STUART Mudd, M.A., M.D., Professor of Bacteriology, Univ. of Pennsylvania. Pp. 272. Springfield, Ill.: Thomas, 1945. Price, $4.50.

THE author has written a very stimulating treatise which will undoubtedly arouse mixed emotions in its readers. Starting with the concept that specific antibody formation is essentially a catalytic or enzyme process, the author has collected and integrated an imposing mass of information. Thus antigens are treated as specific enzymes, antibody precursors as enzyme substrates, and antibodies as specific enzyme inhibitors. Although this idea has been expressed before, here for the first time is an attempt to demonstrate conclusively that the facts fit the criteria of ideal catalysis. As a further extension of this concept the author states: "If . . . we define an enzyme as any protein capable of performing a specialized physiological function in accordance with the well known criteria of ideal catalysis, a comprehensive theory of biocatalysis is provided which links antigens, enzymes, vitamins and hormones and possibly other still unknown substances of similar role." With this concept many will disagree, as the author freely admits. The term enzyme has served in the past as a useful description of proteins which are capable of initiating or stimulating specific catalytic processes in isolated or *in vitro* systems as well as in the complex living organism. To include in this category all proteins exerting a specific biologic effect in the living organism is decidedly a new concept. The Reviewer has no doubt that a splinter driven into the hand will elicit a specific response and might therefore be reasonably called a biocatalyst or even an enzyme. Also, there is surely no need to restrict this all inclusive generalization to proteins. However, this extension of Sevag's ideas to what may appear to be an absurdity does not alter the fact that perhaps the time has come to revise our concepts if only to bring about and stimulate new thought.

The work is divided into 5 main parts: I. Antigens as Biocatalysts; II. Antibody as a Specific Enzyme Inhibitor; III. Anti-enzyme Immunity; IV. Immunity Against Bacterial Enzymes; V. The Problem of Antibody Formation Against Respiratory Enzymes. There is considerable discussion of such interesting topics as antibodies against hydrolytic enzymes, snake venoms, toxins, hemolysins, fibrolysin, hyaluronidase and the relation of these phenomena to the problems of infectious disease.

The book is well written; the printing and binding are excellent. There are a few errors in the organic structures and some loose usage of the terms tautomerism, stereoisomerism, and geometric isomerism. The diagram illustrating the mutarotation of glucose (p. 25) is confusing. These are, however, minor errors which will undoubtedly be corrected in subsequent editions.

This book will be of interest to bacteriologists, immunologists and biochemists. Biochemists, in particular, will find here a stimulating and fertile field for research. It is only fair to state that the underlying concept, based as it is upon chemical principles, is nevertheless a convenient theory and not an accepted fact. Used with reservations, it can serve as a stimulus for new ideas; accepted blindly and without critical judgment, it may lead the unwary into a morass of confusion. It is to the author's credit that he has courageously set forth a challenge and defended it skilfully and honestly. S. G.

MICROBIAL ANTAGONISMS AND ANTIBIOTIC SUBSTANCES. By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers Univ.; Microbiologist, New Jersey Agricultural Experiment Station. Pp. 350 + IX. New York: Commonwealth Fund, 1945. Price, $3.75.

THIS book, the first on the subject of antibiotics, appears at an opportune time to be helpful to those interested in the subject. The material is presented from the biologic viewpoint in a scholarly manner. It compiles and organizes the information on antibiotics. The book describes methods for searching for organisms which show bacterial antagonism, methods for producing antibacterial substances, testing their action against microörganisms and determining possible therapeutic uses. The properties of many antibiotic substances are discussed. The book contains a classification of many antibiotics according to the microörganisms producing them, a glossary of terms used in describing antibiotics, an index of microörganisms cited in the text, a very complete general index and a valuable bibliography of over 1000 citations of the literature. H. M.

MODERN PSYCHIATRY. By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago, Consulting Psychiatrist to Columbus Hosp.; Consultant in Psychiatry, The K. W. Kellogg Foundation; Fellow of the American Psychiatric Association; Member of the American Psychopathologic Association. Pp. 869. St. Louis: Mosby, 1945. Price, $10.00.

COINING the word *personology*, and asserting it should be in the dictionary, the writer proceeds to explain the difficulties human beings have in adjusting themselves to life. The book is for general practitioners, specialists and psychiatrists, and considers the problems of personality maladjustment, the psychoneuroses and psychoses. Its purpose is "a ready and compact reference book for diagnosis and immediate treatment." The Introduction is given over entirely to Psychosomatic Medicine which includes about 25% of the patients who visit physicians. Its 61 chapters are discussed in 4 parts: Personality Problems, The Psychoneuroses, The Psychoses, and General Psychotherapeutics which is given considerable space. The manic-depressive psychoses are accorded more space than any other subject, with the writer saying they result from inherent defects in the nervous system and the metabolic mechanism. A subdivision is manias, depressions and mixed states, each of which undergoes a further subdivision. Among the important hypnotics are sodium amytal and paraldehyde, the former being preferable. It is believed a manic attack can be shortened by deep continuous narcosis with sodium amytal. The schizophrenic reaction type presents the real mystery in psychiatry, with 40,000 new patients occurring annually in the United States, and which constitute about 50% of institution population. When early treatment is instituted, the prognosis is more favorable than formerly. Shock therapy and massive doses of sodium amytal are proving of distinct use. Speaking of the psychoneuroses, the writer estimates that half the patients seen in general practice show more or less neurotic disturbances. "*Never forget!* The average neurotic patient does not really desire to be cured of his neuroticism—he merely wants to secure relief from his numerous distressing and disabling symptoms." After telling of some 15 other theories as to the causes of the neuroses, the writer gives what he terms the Comprehensive Working Theory, embracing at least 3 constant and ever-interlacing factors: (1) Emotional conflict of some sort. (2) Hyperirritability of the vegetative nervous system. (3) Functional and associated endocrine disturbances of varying and ever-changing nature. As to the inferiority complex, stress is laid on the fact that often in early life parents unwittingly cause the child to feel his inferiority; also, a state of chronic discouragement may supervene if too much is expected of the child. The value of narco-analysis of Horsley and others is given scant consideration. In an Appendix the schools of psychiatry are discussed and a Glossary of 34 pages is included. The text covers a vast expanse in psychiatry and is replete with valuable information and stimulating suggestions. N. Y.

THE RETICULO-ENDOTHELIAL SYSTEM IN SULFONAMIDE ACTIVITY. By FRANK THOMAS MAHER, PH.D., Assistant Professor of Pharmacognosy and Pharmacology. Contribution from the Dept. of Pharmacology, Materia Medica, and Therapeutics in the College of Medicine. Pp. 232; numerous figs. and tables. Urbana, Ill.: The Univ. of Illinois Press, 1944. Price, $2.50.

THIS comprises the first 2 numbers of Volume V of University of Illinois Medical and Dental Monographs. It consists of a compilation of the literature bearing on the sulfonamides up to the end of 1941 and a report of the author's own experiments on the influence of blockade of the reticulo-endothelial system (by thorotrast) on the life-saving effects of sulfanilamide and sulfathiazole in rabbits inoculated with streptococci and staphylococci. The results support the general belief that body defense mechanisms play a determining rôle in sulfonamide therapy, but they contribute nothing to an understanding of the factors involved either in the drug action or in the functions of the reticulo-endothelial system. The presentation is extremely detailed and unnecessarily repetitious. The discussions take no account of the work done in this field since 1941 and therefore have more historical than current importance.

C. S.

MEDICAL CLINICS OF NORTH AMERICA. Chicago Number, January 1945. Symposium on Neuropsychiatric Diseases. Pp. 271. Phila.: Saunders. Price, $16.00, year.

THE selection of topics for this symposium was timely. "Discs" are frequently seen in industry and combat operations. Peripheral nerve injury is being inflected too frequently on every battle front. Likewise the Guillian-Barré syndrome is being seen in almost epidemic proportions. The understanding of the psychiatric approach to criminology needs more stress.

The articles are presented clearly, with the possible exception of the *Modern Concept of Schizophrenia*. Only a few omissions can be noted, such as the lack of stress on facial diplegia as part of the Guillian-Barré syndrome and the importance of overlap in peripheral nerve distribution. The electrical reaction of injured nerves was not too clearly put. Especially well presented in the excellent style of the author were the facial pain article by Dr. Walker, subdural hematoma by Dr. Oldberg, insomnia by Dr. Solomon and cordotomy by Dr. Verbrugghen. The articles on myasthenia and periarteritis reviewed the important points in the literature. Electro-shock to out-patients is interesting and well analyzed. This number of the Clinics is a valuable contribution.

J. T.

THE HUMAN MIND. By KARL A. MENNINGER, M.D. Third Ed. Pp. 517; 15 figures. New York: Alfred A. Knopf, 1945. Price, $5.00.

OF the preceding edition, more than 200,000 copies were sold in the United States. The present issue has been "corrected, enlarged and rewritten." The additional matter includes "achievement tests," "alcoholic anonymous," "The American Psychiatric Association," and "electroencephalography." Since an "organic personality type" was mentioned in the 1st edition, the writer now takes pride in his anticipation of psychosomatic medicine though the term is unfortunate, since it implies a duality of mind and body. But little retreat is shown from the previous stand on psychoanalysis as the most important form of mental hygiene. The chapters are: Principles, Personalities, Symptoms, Motives, Treatments and Applications. Though not strictly systematic, a practical and descriptive classification of personalities is given as: crippled, stupid, lonely, queer, and perverse personalities. Under Treatments, while brief reference to "narcosynthesis" is made, the important narco-analysis of Horsley and others, receives no definite consideration. In Symptoms, the dismantled parts of the machine are dealt with analytically. Motives is a dynamic section wherein the source and distribution of the power driving the machine is considered. Treatments, gives the technique of repair making. Applications deals fundamentally with extensions of psychiatric theory.

N. Y.

FUNDAMENTALS OF PHARMACOLOGY. By CLINTON H. THIENES, M.D., PH.D., Professor of Pharmacology, Univ. of Southern California School of Medicine. Pp. 444; 36 figs. New York and London: Hoeber, 1945. Price, $5.75.

THIS concise volume is the textbook on pharmacology in the "Medical Students' Series" designed to "offer the medical student a volume which presents the basis of the subject in such form and degree of detail as he can absorb in the time allotted." It is no easy task to make from a vast wealth of knowledge a selection of fundamental material upon which everyone will unqualifiedly agree. On the whole this book is well and concisely written, logically organized and up to date (including discussions of penicillin, sulfadiazine and thiouracil). It adequately satisfies the need for which it was written.

It must be conceded, however, that this volume or any textbook so conceived accomplishes its objective of brevity only at the sacrifice of information which many in the field would consider important. In the past decade there has been a notable emphasis on the effects of drugs in man, made possible by the development of new methods of clinical investigation; yet this phase of pharmacology appears somewhat neglected. Since data are available on cardiac output and left ventricular work following the administration of therapeutic doses of some important circulatory drugs in man, it would seem well to mention them. The section on renal physiology and diuretics neglects results obtained by techniques now several years old for studying human renal physiology and pharmacology. On the other hand, there is the inclusion and even the emphasis of certain information which could well be left to a more encyclopedic work. Pedagogic technique seems hardly to justify devoting as much space to strychnine, the therapeutic usefulness of which is today thought to be practically *nil*, as to the belladonna group. The consideration of aconite and veratrum and their dosages seems unwarranted. The discussion of toxicology is restricted to substances used therapeutically, so that an important disease like lead poisoning receives no consideration.

In most other respects, however, the book is a worthwhile text and the student who desires a clear, concise and readily assimilable presentation of the subject will find it very useful.

S. K.

TEXTBOOK OF NEUROPATHOLOGY. By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern Univ. Medical School. Second Ed. Pp. 370; 289 ills. New York: Grune & Stratton, 1945. Price, $5.50.

THERE is not great change in the 2nd edition, nor can one expect neuropathology to change greatly in a decade between the 2 editions of this work. It is a clear and concise outline of the macroscopic and microscopic pathology of the nervous system. An interesting feature is the attention given by the author to physical and chemical data pertaining to the brain and its postmortem changes. The new edition takes cognizance of the great strides made in neuropsychiatry through a better understanding of vitamin deficiencies, chemotherapy and shock treatment. Dr. Weil calls attention to the newer conception of the virus infections as well as adding more data on protozoal infections of the nervous system. The 1st edition served as an authoritative text for students and there is every reason to believe that the 2nd edition will be just as popular. The book has been enlarged and 27 plates added.

A. O.

THE BASIS OF CLINICAL NEUROLOGY. The Anatomy and Physiology of the Nervous System in Their Application to Clinical Neurology. By SAMUEL BROCK, M.D., Professor of Neurology, College of Medicine, New York Univ. Second Ed. Pp. 393; 72 figs. Baltimore: Williams & Wilkins, 1945. Price, $5.50.

THIS 2nd edition of Dr. Brock's deservedly vaunted book has been rather extensively revised because of the great advances in neurophysiology produced

by laboratory investigators and neurosurgeons. He has, as in the 1st edition, maintained the emphasis on the clinical application of the newer knowledge gained both in neurophysiology and neuroanatomy. In their respective chapters 3 collaborators have added electrodiagnostic methods, physiology of urination and cystometry and electroencephalography, respectively. The amplified text reflects the author's extensive experience as a clinician and his keen appreciation of clinical phenomena. This combined with the morphology, physiology and pathology of the nervous system makes the work an invaluable guide to the sound and practical interpretation of nervous diseases. From this standpoint it is an unusual book on clinical neurology worthy of the close attention of student, clinician and teacher alike. A. O.

COMMON AILMENTS OF MAN. Edited by MORRIS FISHBEIN, M.D., Editor, Hygeia, The Health Magazine. Pp. 177. New York: Garden City Publ. Co., 9th Copyright, 1945. Price, $1.00.

THIS is the 9th of a series of reprints from *Hygeia*, the American Medical Association's health magazine for the public. The 16 articles cover our commonest ailments and symptoms—a good half having been written by nationally recognized authorities. Carefully warning against the error of improper self treatment, they should be helpful in informing the layman to understand his physical ailments and to know when to seek expert help. E. K.

MEN UNDER STRESS. By ROY R. GRINKER, LT. COL., M.C., and JOHN P. SPIEGEL, MAJOR, M.C. Pp. 484; 2 tables. Phila.: Blakiston, 1945. Price, $5.00.

THE first Army Air Forces convalescent hospital in this country, caring exclusively for "Operational Fatigue" sufferers, was established by these authors. Though several thousand cases were seen by them, lack of space has prevented the recording of but 65; a number of their subjects were given sodium pentothal to facilitate abreaction, then following with appropriate psychotherapy. The text is discussed in the following Parts: The Man; The Environment of Combat; The Reactions to Combat—Morale; The Reactions After Combat; Civilian Applications. Reactions After Combat is most important and is treated as: The Return Home; The Syndrome of "Operational Fatigue" (war neuroses) in Returnees; Passive-Dependent States; Psychosomatic States; Guilt and Depression; Aggressive and Hostile Reactions; Psychotic-like States; Psychodynamics; Psychotherapy; Narcosynthesis; Adjunctive Treatment, and Results.

In regard to narcosynthesis: when time permits, psychiatric interviews while the patient is fully conscious, yields the necessary material and emotional release; but during combat, a shortcut is necessary, and in approximately half of their subjects, such a procedure was required. The drug of choice is sodium pentothal, which acts more promptly than other drugs; a slow intravenous injection is made until the proper stage of narcosis is obtained. Alcoholics do not respond satisfactorily, so that patients must not drink for hours before the injection. Skill is required to obtain the best results. The information gained by shortening the time should be of value in civilian psychiatry. Narcosis, or continuous sleep treatment, was not promising; the drug of choice is sodium amytal; the duration of sleep varied from 27 to 110 hours. Of 20 patients so treated, only 3 showed improvement, and the rest were unimproved or made worse.

As the number of subjects needing treatment is large, and as recreational and occupational therapy are not sufficient for the needs of many, *group psychotherapy* is being widely employed; for this, some special training is required. Two methods are employed: in the repressive-inspirational method, the effort is to "urge, persuade and force the patient to control himself, to suppress asocial or worrisome thoughts. Interest or inspiration in life work, the community, religion, art, music, etc., is encouraged." The analytic method

"urges the loosening of repression and feeling of urges bound up in repression. It strives for the conscious recognition and analysis of unconscious and asocial wishes and trends." The 2 methods may be combined. This book is timely and important. N. Y.

CLINICAL ATLAS OF BLOOD DISEASES. By A. PINEY, M.D., M.R.C.P., Physician, St. Mary's Hospital for Women and Children; and STANLEY WYARD, M.D., F.R.C.P., Physician, The Royal Cancer Hospital, London, and Princess Beatrice Hospital. Sixth Ed. With 48 illustrations, 45 in color.

THIS practical guide, by the use of "telegraphic" style consistently followed, and oriented by different kinds of type, gives valuable help to the busy practitioner. The authoritative authorship and the many colored plates (somewhat too diagrammatic) with a synopsis of the symptoms, diagnosis, pathodiagnosis, etiology, pathology, and treatment opposite each plate, still further add to its usefulness. E. K.

THE MALE HORMONE. By PAUL DE KRUIF. New York: Harcourt, Brace & Co., 1945. Price, $2.50.

IF this book confined itself to telling, as the cover states, "without blushes or polite evasions the story of the discovery of the male hormone," it would not be subject to blame, nor would it be a "best seller." But when, again to quote from the cover, "It boosts muscle power. It banishes mental fatigue. It eases heart pain. It even restores the sanity of men in midlife who suffer male hormone hunger; seems to renew the tissues of ageing men. It brings a gleam of hope for the extension of the working, vigorous lives of millions of Americans," then it exceeds the bounds of propriety and of legitimate popular medicine writing. Testosterone is known to be a potent drug and its therapeutic values are being studied by many investigators. However, these are far from being established in all the conditions quoted above and we know little or nothing of its capacity to do harm. If the author with his considerable medical knowledge chooses to use it on himself that is his own affair. But when a man with his following advertises a potentially dangerous drug in this way to a public who is incapable of weighing the pros and cons—for motives known only to himself—he takes a step which most medical men and other intelligent people regard as unjustified, improper and potentially harmful. E. K.

FRANCOIS MAGENDIE. By J. M. D. OLMSTED, Professor of Physiology, University of California. Preface by JOHN F. FULTON. Pp. 290; illustrated. New York: Schuman, 1945. Price, $5.00.

MAGENDIE appeared on the French medical scene when France led the world, in both scientific and clinical medicine. Overshadowed by his greater pupil, Claude Bernard, his truly great contributions have tended to be overlooked. The founder of French experimental physiology, he was an early member of that great band who demanded the evidence even though at times his own studies led to unwarranted speculation. His demonstration that the anterior spinal nerve roots were motor and the posterior sensory provoked the long controversy with Charles Bell—given in detail in Dr. Olmsted's work—and led to further studies on the central nervous system, sensibility and irritability which brought him into conflict with Flourlen. One might add that the tendency to controversy among medical scientists was near its peak in the early 19th century. One also reads of Magendie's experimental study of poisons, called the beginning of experimental pharmacology, of his revolt from Bichat, of his famous Formulary, which went through many editions and translations, of his founding the *Journal de physiologie expérimental*, of his studies of the cerebrospinal fluid, of his collaboration with Claude Bernard, of his efforts in the cholera epidemic, of his late "arrival" in a chair at the College de France and at a post at the Hotel Dieu and of various honors from the outerworld. We are indebted to Dr. Olmsted for this new study of a great French physiologist, and join with Dr. Fulton in the hope that others such as Brown-Séquard may later be included in the group. E. K.

A Synopsis of Medicine. By Sir Henry Letheby Tidy, K.B.E., M.A., B.Ch. (Oxon.), F.R.C.P. (Lond.), Extra Physician to H.M. The King; Consulting Physician to St. Thomas's Hospital; Hon. Major-General, lately Consulting Physician to the British Army. Eighth Ed. Baltimore: Williams & Wilkins, 1945. Price, $7.50.

As a *multum in parvo* ready reference desk book, Tidy's Synopsis offers an extraordinary amount of pertinent information in readily available form. The consistent use of various kinds and sizes of type, and a reasonable constancy in the order of presentation (etiology, morbid anatomy, symptoms, progress, termination, diagnosis, treatment, with occasional historical notes) considerably increase "availability," and so are especially desirable in books of this kind. This availability is further supplemented by a really adequate index of 71 pages, in small, but legible type. This edition contains the expected number of new articles, amplifications, and revisions that medical progress has necessitated. These are enumerated in the Preface. This should be read also as an indication of the wisdom that has guided the selection of items to be included and to illustrate excellent phraseology, which is apparent even in the restricted circumstances of a work of this kind. The book has already found its place on the surface of the Reviewer's desk.

E. K.

NEW BOOKS

Men Under Stress. By Lt. Col. Roy R. Grinker, M.C., and Major John P. Spiegel, M.C., Army Air Forces. Pp. 484. Phila.: Blakiston, 1945. Price, $5.00. (Reviewed on page 277.)

Science in Progress. Fourth Series. Edited by George A. Baitsell. 11 Contributors. Pp. 331; 106 figs. New Haven: Yale Univ. Press, 1945. Price, $3.00.

The 18th anniversary issue, Vol. I, 1945, of the *Harofe Haivri* (*The Hebrew Medical Journal*), edited by Moses Einhorn, M.D., is a special issue dedicated to the late Henrietta Szold, distinguished humanist and Zionist who interested American Jewish womanhood in Hadassah, a great organization responsible for the medical and sanitary installations in Palestine. Since 1939 Hadassah has coöperated to the maximum with the Medical Military Forces stationed in Palestine and Near East. Special courses and clinical conferences on tropical and subtropical diseases, war surgery, typhus fever, malnutrition, etc., have been made available at the Rothschild-Hadassah-University Hospital. In addition, Hadassah's Malaria Control Service is said to have rendered Palestine the only country in this part of the world in which this infectious disease is of minor significance as a factor in troop morbidity.

Hayfever Plants. Their Appearance, Distribution, Time of Flowering, and Their Rôle in Hayfever, With Special Reference to North America. By Roger P. Wodehouse, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, N. Y. Pp. 245; various figs. and tables. Waltham, Mass.: Chronica Botanica Co.; New York City: G. E. Stechert & Co., 1945. Price, $4.75.

A Handbook of Psychiatry. By Louis J. Karnosh, B.S., Sc.D., M.D., Associate Clinical Professor of Nervous Diseases, School of Medicine, Western Reserve Univ.; Director of Neuropsychiatry, City Hospital, Cleveland. With the collaboration of Edward M. Zucker, A.B., M.D., Clinical Instructor in Nervous Diseases, Western Reserve School of Medicine; Associate in Neuropsychiatry at Cleveland City Hospital. Pp. 302; 38 figs. St. Louis: Mosby, 1945. Price, $4.50.

Thoughts, Deeds and Human Happiness. By K. W. Monsarrat. Pp. 123. London, England: Hodder & Stoughton, 1944. Price, 7/6 ($1.50).

Trabalhos do Departamento de Anatomia Patologica (25 reprints). Faculdade de Medicina da Universidade de São Paulo. Volumes XVI–XVII–XVIII. Diretor Prof. Dr. Ludgero da Cunha Motta. 1945.

NEW EDITIONS

An Index of Differential Diagnosis of Main Symptoms. By Various Writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (OXON.), F.R.C.P., Consulting Physician, Guy's Hosp.; late Physician, H.M. Household. Assisted by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Physician, Guy's Hosp.; Honorary Physician, All Saints' Hosp. for Genito-urinary Diseases. Sixth Ed. Pp. 1128; 798 ills. of which 231 are colored. Baltimore: Williams & Wilkins, 1945.

Handbook of Practical Bacteriology. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, C.B.E., M.D., D.P.H., Professor of Bacteriology, Univ. of Edinburgh; Honorary Bacteriologist to the Royal Infirmary, Edinburgh; and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, London County Council; Major, R.A.M.C. Seventh Ed. Pp. 720. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Physician, St. Mary's Hosp. for Women and Children; and STANLEY WYARD, M.D., F.R.C.P., Physician, The Royal Cancer Hosp., London, and Princess Beatrice Hosp. Sixth Ed. Pp. 137; with 48 ills., 45 in color. Phila.: Blakiston, 1945. Price, $5.00.

Refraction of the Eye. By ALFRED COWAN, M.D., Professor of Ophthalmology, Graduate School of Medicine, Univ. of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hosp.; Consulting Ophthalmologist, Council for the Blind and Supervising Ophthalmologist of the Dept. of Public Assistance, Commonwealth of Pennsylvania. Second Ed. Pp. 278; 172 engravings and 3 colored plates. Phila.: Lea & Febiger, 1945. Price, $4.75

CORRECTION

In Capt. E. R. Movitt's article "Spontaneous Pneumothorax as a Complication of Pneumonia in Adults" in our May 1945 number under the report of cases, Case 2, fourth paragraph, the dosage of Cedilanid should be as follows: "Six cc. of *Cedilanid* (1.2 mg.)"

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

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